A STUDY OF PREVALENCE OF BACTERIAL INFECTION IN PATIENTS WITH LIVER CIRRHOSIS – A CROSS – SECTIONAL STUDY

A Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI

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For the Award of the Degree of

M.D (General Medicine)

Branch-I

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BONAFIDE CERTIFICATE

This is to certify that "A **STUDY OF PREVALENCE OF BACTERIAL INFECTION IN PATIENTS WITH LIVER CIRRHOSIS – A CROSS-SECTIONAL STUDY"** is a bonafide work done by **Dr. P.PARTHIBAN**, Post graduate student, Department of General Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in partial fulfillment of rules and regulations of the Tamil Nadu Dr. M.G.R Medical University, for the award of M.D. Degree Branch I (General Medicine) during the academic period from May 2015 to April 2018.

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DECLARATION

I hereby declare that this dissertation titled **"A STUDY OF PREVALENCE OF BACTERIAL INFECTION IN PATIENT WITH LIVER CIRRHOSIS" at Govt. Kilpauk Medical College Hospital."** is a bonafide and genuine research work carried out by me in the Department of General Medicine, Government Kilpauk Medical and Hospital, Chennai-10, under the guidance of our Chief**. Prof. Dr. K.E. GOVINDARAJULU M.D,** Government Kilpauk Medical College and Hospital.

This dissertation is submitted to **THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI** in partial fulfillment of the University regulations for the award of M.D degree (General Medicine) Branch I.

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The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "**Study of Bacterial Infection in Patients with Liver Cirrhosis"** submitted by Dr.P.Parthiban, M.D. (General Medicine), PG Student, GKMC, Chennai-10

The Proposal is APPROVED

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

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ABBREVIATIONS

ACLF	-	Acute on chronic liver failure
AF	-	Ascitic fluid
ALP	-	Alkaline phosphatase
ALT	-	Alanine transaminase
AKI	-	Acute kidney injury
AKIN	-	Acute kidney injury network
AST	-	Aspartate transaminase
BT	-	Bacterial translocation
CAID	-	Cirrhosis associated immune dysfunction
C.difficile	-	Clostridium difficile
CDAD	-	Clostridium difficile associated diarrhoea
CLIF	-	Chronic liver failure
CNNA	-	Culture negative neutrocytic ascites
CRP	-	C-reactive protein
CTP	-	Child-Turcotte Pugh
DALY	-	Disability adjusted life years
DAMP	-	Damage associated molecular patterns
DIC	-	Disseminated intravascular coagulation
DST	-	Direct susceptibility testing
EASL	-	European association for the study of the liver
E.coli	-	Escherichia coli

ESBL	-	Extended spectrum β-lactamase
GI	-	Gastrointestinal
HCl	-	Hydrochloric acid
HE	-	Hepatic encephalopathy
HRS	-	Hepato renal syndrome
IBO	-	Intestinal bacterial overgrowth
IE	-	Infective endocarditis
INR	-	International normalized ratio
K.pneumoniae	-	Klebsiella pneumoniae
LPS	-	Lipopolysaccharide
MALDI-TOF	-	Matrix assisted laser desorption ionization-time of flight
MAMP	-	Microbial associated molecular patterns
MELD	-	Model for end stage liver disease
MLN	-	Mesenteric lymph nodes
MNMB	-	Monobacterial non-neutrocytic bacteriascites
MR	-	Multidrug resistant
MR-proADM	-	Midregion-proAdrenomedullin
MRSA	-	Multidrug resistant Staphylococcus aureus
NACSELD	-	North American consortium for study of end-stage liver disease
NFκβ	-	Nuclear factor κβ
NK-cell	-	Natural killer cell
NIS	-	Nationwide in-patient sample
NLR	-	NOD like receptor

NSBB	-	Nonspecific beta blocker
PCR	-	Polymerase chain reaction
PCT	-	Procalcitonin
PMN	-	Polymorphonuclear
PT	-	Prothrombin time
RAI	-	Relative adrenal insufficiency
RCT	-	Randomised control trial
SBP	-	Spontaneous bacterial peritonitis
SBEM	-	Spontaneous bacterial empyema
SIRS	-	Systemic inflammatory response syndrome
SOFA	-	Sequential organ failure assessment
Spp.	-	Species pluralis (latin)
SSTI	-	Skin and soft tissue infections
TIPSS	-	Transjugular intra hepatic portosystemic shunt
TJ	-	Tight junctions
TNF-α	-	Tumour necrosis factor-α
TLC	-	Total leucocyte count
TLR	-	Toll-like receptor
UTI	-	Urinary tract infection
vWF	-	von-Willebrand factor

CONTENTS

INTRODUCTION

Cirrhosis is a condition that is characterized by regenerative nodules and fibrosis in the liver and has a variety of clinical manifestations and complications, some of which are life-threatening. Regardless of the cause, cirrhosis evolves to the point when there is architectural distortion and formation of regenerative nodules. Features of cirrhosis are a result of the pathological changes and are a measure of the severity of the disease.[1]

The distortion of liver parenchyma results in increased resistance to portal blood flow and leads to portal hypertension and hepatic synthetic dysfunction.[1,2] Splanchnic vasodilation with a increase in the inflow of blood into the portal venous system contributes to the increase in portal pressure.[3] Splanchnic vasodilation is an adaptive response to the changes in intrahepatic hemodynamics in this case ; its mechanisms are directly opposite to those of the increased hepatic vascular tone. Increased portal pressure and splanchnic vasodilation together cause the various complications of liver cirrhosis like formation of porto -systemic collaterals with development of esophageal varices and subsequent variceal bleeding, ascites, hepatorenal syndrome, hepatopulmonary syndrome, portopulmonary hypertension and hepatic encephalopathy.[3]

The causes of cirrhosis in the more developed countries are infection with hepatitis C virus, alcohol abuse, and, increasingly, non-alcoholic fatty liver disease; infection with hepatitis B virus is the most common cause in sub-Saharan Africa and most parts of Asia. The prevalence of cirrhosis is difficult to assess and is probably higher than reported, because the initial stages are asymptomatic;.[3]

Clinically, cirrhosis has been regarded as an end-stage disease that invariably leads to death unless liver transplantation is done, and the only preventive strategies have been screening for oesophageal varices and hepatocellular carcinoma. Lately, this perception has been challenged, because 1-year mortality in cirrhosis varies widely, from 1% to 57%, depending on the occurrence of clinical decompensating events.[4]

Acute decompensating events leading to organ failure have a mortality of 30%; mortality is higher in previously compensated patients than in those with previous decompensation, which suggests greater tolerance of the latter through the effects of the inflammatory response.[5] Decompensating events are generally triggered by precipitating factors that are infection, portal vein thrombosis, surgery, and hepatocellular carcinoma.

Liver cirrhosis has emerged as a major cause of global health burden. According to the Global Burden of Disease study reported in 2012, liver cirrhosis caused 32.56 million disability adjusted life years (DALYs); 1.1% of the total.[6] Global Burden of Disease Study (2013) reported that years lived with disability (YLD) due to cirrhosis was 544,600 and percentage change from 1990 to 2013 was 29.2%.[7] In a study by Mokdad AA et al, which assessed liver cirrhosis mortality in 187 countries between 1980 and 2010, it was found the mortality due to cirrhosis was progressively increasing. Even though newer drugs and treatment modalities have decreased death due to Hepatitis B and C, alcoholic liver disease and the resultant cirrhosis continue to claim more lives. In India, all-cause mortality due to liver cirrhosis has increased from 77,741 in 1980 to 188,575 in 2010.[8]

Bacterial infections are positive in 25% to 47% patients who are diagnosed with a diagnosis of cirrhosis[9-12] and represent the most important precipitating event for acute decompensation.[5] Infections are increasingly recognized as an important stimulating factor for systemic inflammation and organ failure in late cirrhosis leading to a four-fold increase in mortality.[13] Despite recent advances in understanding the underlying pathogenic mechanisms of bacterial infections in cirrhosis,[14-16] the growth of infections to multiple organ failure and septic shock is associated with a short-term mortality exceeding 75%.[5]

Early diagnosis and treatment of infections are of paramount importance for the management of patients with decompensated cirrhosis, bacterial infections are important causes of morbidity and mortality in the cirrhosis patients.[17] The consequences of infection include prolonged hospitalization, acute kidney injury (AKI), death, de-listing from liver transplant and victim to further infections.[18] Out of the 26,300 hospitalized cirrhotics, who required ICU admission, studied in the 2006 US nationwide sample, there were 13,800 deaths, a death of 53%, making early diagnosis and treatment of utmost importance.[18] The most accepted reason for the development of bacterial infections in decompensated liver disease is the translocation of gut microbial flora.

There are not many studies on bacterial infections in cirrhotic patients in the Indian context. Hence we planned the study to assess the prevalence of bacterial infections in patients with cirrhosis. We also studied the factors associated with infections, so that patients susceptible to infections could be identified early and treated promptly.

REVIEW OF LITERATURE

BACKGROUND

The word ‘cirrhosis’ is derived from the Greek word ‘kirros’ meaning yellow-tan (tawny), which is the normal color of the liver in this condition. Cirrhosis results from different causes of liver injury that lead to necroinflammation and fibrogenesis; histologically it is characterised by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, causing pronounced distortion of hepatic vascular architecture.[1,2] This distortion results in increased resistance to portal blood flow causing portal hypertension and hepatic synthetic dysfunction.[1,2]

ETIOLOGY OF CIRRHOSIS

Cirrhosis can arise as a consequence of an exogenous, toxic, infectious, allergic, immunopathological, autoimmune, or vascular process or an inborn error of metabolism.

The causes of cirrhosis can be classified as follows[19]:

1. Fatty liver disease
    - Alcoholic liver disease
    - Non-alcoholic fatty liver disease
2. Viral
    - Hepatitis B
    - Hepatitis C
    - Hepatitis D
3. Storage diseases
    - Hemochromatosis

- Wilson’s disease
- α- 1 antitrypsin deficiency

4. Cardiovascular
    - Budd-Chiari syndrome
    - Right heart failure
5. Autoimmune
    - Autoimmune hepatitis
    - Primary biliary cirrhosis
    - Primary sclerosing cholangitis
    - IgG4 cholangiopathy
6. Chronic biliary diseases
    - Recurrent bacterial cholangitis
    - Bile duct stenosis
7. Rare
    - Drug induced
    - Porphyria

CLINICAL MANIFESTATIONS OF CIRRHOSIS

Decompensated cirrhosis can present with abdominal swelling, jaundice, and gastrointestinal bleeding. Physical examination includes a contracted, nodular liver, splenomegaly, ascites, dilated abdominal wall veins, spider angiomas, palmar erythema, peripheral edema and asterixis. Patients may be diagnosed accidentally through laboratory findings. Elevated levels of alanine transaminase and/or aspartate transaminase can mean hepatocyte injury; however, these may be normal with advanced liver disease. Elevation of prothrombin time or International Normalized

Ratio (INR) may show a decreased ability of the liver to synthesize clotting factors. Thrombocytopenia indicates the splenic sequestration. The total bilirubin level may or may not be elevated.[20]

COMPLICATIONS OF CIRRHOSIS:

Liver parenchymal distortion, increased portal venous pressure and splanchnic vasodilation lead to the majority of complications of cirrhosis.[3]

1. Portal hypertension
    - Oesophageal varices
    - Portal hypertensive gastropathy
    - Splenomegaly and hypersplenism
    - Ascites and in turn, spontaneous bacterial peritonitis
2. Hepatorenal syndrome (Types 1 and 2)
3. Hepatic encephalopathy
4. Hepatopulmonary syndrome
5. Portopulmonary hypertension

Liver cirrhosis compromises the synthetic functions of the liver and can lead to the following complications and conditions.[3]

1. Malnutrition
2. Coagulopathy
3. Bone disease (osteopenia, osteoporosis and osteomalacia)

Patients with cirrhosis who are hospitalized for an acute decompensation and also have organ failures are at high risk of short-term death and lose their life. These patients have a syndrome called Acute-on-Chronic Liver Failure (ACLF).[5] Bacterial

infections are found to be one of the common causes of decompensation in liver cirrhosis and are a leading cause of mortality and acute-on-chronic liver failure. The main problem with the diagnosis of infections in cirrhosis is the underlying partial systemic inflammatory response syndrome (SIRS) state and negative cultures in 30–50% of cirrhotic patients. More information regarding the modulation of infections by the underlying immune state, gut barrier function and super-imposed medications such as β-blockers, proton pump inhibitors and antibiotics is still required. The emergence of multi-drug resistant organisms and *Clostridium difficile* has also recently changed the approach for prophylaxis and therapy of infections. Effective strategies for the prevention, diagnosis, and management of infections in cirrhosis forms a basic method in the treatment.[18]

Various trials have found that infections are present in 25-47% of all hospitalised patients with cirrhosis. A prospective study by Caly WR et al reported in 1993 that bacterial infections were present in 80 out of 170 (47%) of patients with cirrhosis. Among them, the frequent types of infection were: spontaneous bacterial peritonitis (SBP): 31.07%, urinary tract infection (UTI): 25.24% and pneumonia: 21.37%. Community acquired infections were more frequent (56.25%) than nosocomial infections (32.50%) and they occurred sequentially in 11.25% of the cases. The agents responsible are Gram negative bacteria in 72.34% of the infected cases.

A multicenter prospective study by Borzio M et al calculated a total of 405 consecutive admissions in 361 patients (249 males and 112 females; 66 Child-Pugh class B and 295 class C). The study documented bacterial infections in 150 out of 405 patients with cirrhosis (34%) of which 89 were community acquired and 61 were

health-care associated. Urinary tract (41%), ascites (23%), blood (21%) and respiratory tract (17%) are the most common sites of infection.[10]

In a study by Fernández J et al, a total of 1567 admissions of cirrhotic patients were studied. 572 bacterial infections were diagnosed in 507 admissions (32%). Out of the 572 infections, 138 were SBP (24.12%), 111 were UTI (19.4%), 78 were pneumonia (13.63%) and 45 were bacteremia (7.86%). Other infections were culture-negative fever associated with leukocytosis (56 cases), cellulitis (34 cases), spontaneous bacteremia (28 cases), cholangitis (21 cases), secondary peritonitis (19 cases), purulent bronchitis (16 cases), spontaneous bacterial empyema (9 cases), endocarditis (8 cases), bacterascites in the setting of fever and leukocytosis (5 cases), and gastroenteritis (4 cases) was the study results.[11]

In a study conducted in Argentina by Mathurin S et al, a total of 211 consecutive admissions in 132 cirrhotic patients, between April 2004 and July 2007, were included. 129 episodes of bacterial infections were diagnosed in 99 of the 211 (46.9%) admissions; community-acquired in 79 (61.2%) and hospital-acquired in 50 (38.8%). They included spontaneous bacterial peritonitis (23.3%), urinary tract infection (21.7%), pneumonia (17.8%), infection of the skin and soft parts (17.1%), sepsis by spontaneous bacteremia (7.7%), other bacterial infections (12.4%). Gram-positive organisms were responsible for 52.2% of the documented cases with the cirrhosis.[21]

In a retrospective study by Preda CM et al reported in 2011, 1046 patients of cirrhosis were studied. 51 patients (4.9%) were found with bacterial infections. In one patient, infections were located in three sites: peritoneal, blood and urine, and in 7 patients infections were located in 2 sites. Bacterial infections were localized to the following sites: peritoneal- 26 cases, urinary- 20 cases, pneumonia- 8 cases, skin- 4

cases and bacteremia- 1 case. In this study the rate of bacterial infections was low compared to the existing literature (4.9% vs. 15-30%), because the study was retrospective, severe infections were only recorded .[22]

In a Korean study (2011) which studied the outcomes of bacteremia in patients with liver cirrhosis, a total of 195 patients of liver cirrhosis were compared with 1659 patients with other underlying diseases. Intra-abdominal infections were more frequent on cirrhosis, while pneumonia, urinary tract bacteremia, and primary bacteremia are more prevalent in the other diseases group. Patients with cirrhosis were more likely to have *K. pneumoniae* bacteremia compared to coagulase negative staphylococcal bacteremia. Multivariate analysis revealed cirrhosis to be a predictor of mortality in the presence of infections.[23]

With the development of sepsis, mortality increases slightly more than 50%.[10-12] It has been demonstrated that there is a fourfold increased risk of death in infected cirrhotic patients analysed with their non-infected counterparts.[13] While the mortality rates of most diseases have decreased with modern medical advancements, the mortality of patients with cirrhosis has remained unchanged.[24] Bacterial infections in patients with end-stage liver disease also affect candidacy for liver transplantation.

The extent of infections in cirrhosis is not easily quantifiable because of many confounding factors. From the study by Runyon BA et al in 1988, it was found that almost 30–50% of infections, such as spontaneous bacterial peritonitis (SBP), can remain culture negative.[25] Also a partial SIRS-like state is present in most patients with decompensated cirrhosis and so cannot be used to identify infections.[26] Measuring C-reactive protein and procalcitonin may be helpful in selected patients, but a specific marker is still needed.[27,28] A heightened suspicion of potentially resistant organisms is also required in order to change therapy as needed.[12] There are

limited data on the emergence of multi resistant strains and healthcare-associated (which develop <48 h after admission in patients with previous exposure to healthcare services in the preceding 90 or 180 days) and nosocomial (which develop >48 h after admission) infections.[18]

An idea of the magnitude of the problem may be obtained from the US nationwide in-patient sample (NIS). The NIS identified 65,072 patients in 2006 with a discharge diagnosis of cirrhosis. The total costs incurred were approximately US$14 billion per year. Of those 26,300 had presumed infection and required ICU support. The in-house mortality of the hospitalised cirrhotic patients was 53%, or 13 800 deaths a year. The gravity of the situation is dire and cannot be over-emphasised.[18]

The North American Consortium for the Study of End-Stage Liver Disease (NACSELD) study done by Bajaj J et al, which focused on determining the outcome of infections in cirrhosis found out that the majority of infections were spontaneous bacterial peritonitis (SBP) and urinary tract infection (UTI), followed by spontaneous bacteremia, skin, *C. difficile* infections.[29] Gram-positive (36%) organisms were the most common, followed by Gram-negative (30%) organisms. The remainder was either fungal (4%) in origin or infections without an isolated organism. Mortality was high for respiratory infections, bacteremia and *C. difficile* infections, and lowest for urinary and skin infections or SBP. 56% the infections were healthcare-associated, 20% nosocomial, and importantly, 28% of patients developed a second infection during hospitalisation. The overall mortality was 25%, and patients who died had a higher Model for End-Stage Liver Disease (MELD) score at admission and were more likely to have hepatic encephalopathy (HE), hepatorenal syndrome (HRS), mechanical ventilation and ICU stay during hospitalization.[29]

A similar study conducted in Spain by Fernandez J et al which studied 669 infections in 2 series (2005–2007 and 2010–2011) found that hospital mortality rate of nosocomial infections (25–48% respectively) were high than that observed in health-care associated (9–23% respectively) and community-acquired episodes (7–21% respectively). The study also showed that nosocomial infections caused by multidrug resistant bacteria are more common and have a poorer prognosis.[12]

PATHOGENESIS:

The pathogenetic mechanisms for most bacterial infections seen in cirrhosis are as follows.[30]

1. Interaction of gut microbiota and host immune system
2. Intestinal barrier dysfunction
3. Genetic susceptibility to bacterial infections
4. Immune dysfunction

INTERACTION OF GUT MICROBIOTA AND HOST IMMUNE SYSTEM:

Bacterial translocation (BT) from the gut occurs into mesenteric lymph nodes even in healthy individuals and is increased in cirrhosis and hence is called pathological BT. The interaction between host's gut-associated lymphatic tissue and gut bacteria plays a key role in keeping pathological BT under check. An imbalance of this delicate homeostasis between host and gut microbiota can lead to BT and infections.[31] This imbalance can be either quantitative (intestinal bacterial overgrowth – IBO) or qualitative (dysbiosis). IBO occurs mostly in the small intestine,[32,33] is multifactorial, and contributing factors include decrease in gastric acid secretion, decrease in intestinal motility, lack of bile constituents and antimicrobial peptides as well as portal hypertension.[34-39] Patients with cirrhosis and IBO more frequently have

SBP than patients without bacterial overgrowth.[34] Experimental studies by Kalambokis et al (2012) and Madrid et al (2001) have proved that reducing the intestinal bacterial burden with antibiotics decreases liver disease severity and infections in patients with cirrhosis.[40,41] Qualitative changes of the human microbiome, characterized by deep pyrosequencing have also been implicated in these infections.[42]

Among the gut bacteria, Gram negative enteric bacilli more easily translocate to mesenteric lymph nodes (MLN) than Gram positive bacteria and obligate anaerobes.[43] Although the ability to translocate varies between different *Escherichia coli* (*E. coli*) strains, no single virulence factor responsible for BT has been identified.[44] Furthermore, catabolic and inflammatory stress to the epithelial barrier can increase BT of various coliform strains.[45,46] In a study by Cirera et al involving 101 cirrhotic patients and 35 non-cirrhotic patients, it was found that with classical bacterial culture techniques, enteric organisms can be detected in MLN from up to 30% of patients with Child-Pugh class C cirrhosis compared to 9%-15% of non-cirrhotic patients.[47,48] Based on studies by Lu et al (2011) and Liu et al (2004), there is evidence that the fecal microbiome in cirrhosis is less diverse and shows an abundance of *Enterobacteriaceae, Streptococcus* spp. and *Enterococcus faecalis,*[49,50] which mirrors the microbial pattern observed in SBP.[51,52] It has also been observed that the enrichment of *Enterococcus, Proteus, Clostridium,* and *Burkholderia* in the colonic mucosa and the loss of commensal bacteria in cirrhosis was associated with more severe liver disease, increased inflammation and endothelial activation.[42,53] Recent findings showing that the gut microbiome is modulated by the enterocyte inflammasome[54,55] which leads to increased BT and assisted hepatic inflammation,[56]

suggesting a critical interaction of gut mucosa, intestinal dysbiosis and immune activation in cirrhosis.

INTESTINAL BARRIER DYSFUNCTION:

Increased intestinal permeability has been demonstrated in advanced liver disease with septic complications.[57] A study by Assimakopolous in 2013 that was aimed at uncovering the molecular events associated with increased intestinal permeability found that alterations in Tight junction (TJ) proteins are present in cirrhosis and most likely loosen the TJs.[58] Transcytosis appears to be the predominant mechanism by which translocation takes place but is poorly defined in cirrhosis. Tumor necrosis factor-α (TNF-α), a key regulator modulating TJ and transcytosis, is increased in the gut-associated lymphatic tissue in advanced cirrhosis.[59]. They include IgA,[60] biliary lipids,[61] and antimicrobial peptides like REG3G.[38] Altered Paneth cell activity has also been observed in cirrhosis, with decreased mucosal killing activity against invading bacteria.[38]

GENETIC SUSCEPTIBILITY TO BACTERIAL INFECTIONS:

Extracellular bacteria are recognized by membrane-bound Toll-like receptors (TLR) and intracellular Nod-like receptors (NLR), including NOD2 and NLRP3, which lead to activation of nuclear factor NFKβ and stimulate the release of antimicrobial peptides.[57] TLR1 and TLR2 recognize tri-acylated lipoprotein from Gram positive bacteria, TLR4 detects lipopolysaccharide (LPS), and NOD2 senses muramyl dipeptide, a cell wall component of gram negative bacteria. TLR4-deficient mice have been found to have less severe fulminant hepatitis and ischemic-reperfusion injury compared to normal mice.[62,63] In a study by Appenrodt et al (2010) in 150 patients of cirrhosis who carried NOD2 gene variants, it was shown that they

displayed a higher risk for culture positive SBP,[64] variceal bleeding, hepatocellular carcinoma[65] and death. In addition, SBP, caused mostly by Gram positive bacteria was more frequent in patients who carry TLR2 risk variants (Nischalke et al, 2011).[66] These genetic variants were associated with surrogate markers for abnormal intestinal permeability and BT. These studies show that common gene variants linked to impaired mucosal barrier function and BT represent risk factors for SBP and other infections in patients with cirrhosis.

IMMUNE DYSFUNCTION:

Cirrhosis associated immune dysfunction (CAID) involves a state of concurrent immunodeficiency, and persistent activation of the immune system cells with production of pro-inflammatory cytokines.[67-9] Immunodeficiency affects both the innate and the adaptive arm of the immune system. Except for monocytes, cirrhosis leads to reduced numbers of circulating immune system cells, especially neutrophils, naïve helper-T, cytotoxic T-cells and CD27+ memory B-cells.[70] Mononuclear phagocytic cells and neutrophils also show reduced abilities of phagocytosis and mobilization, T and B cells show hypo-proliferation in response to mitogens and NK cells display low cytotoxic activity.[71-3] Cirrhosis leads to reduced number of liver reticuloendothelial mononuclear cells in liver and porto-systemic shunting, which lowers the liver's ability to clear intestinal bacteria. It also causes decreased hepatic synthesis of complement factors and also secreted-pattern recognition receptors.[74] These defects coexist with an induced expression of activation molecules and \increased synthesis of pro-inflammatory cytokines, especially by monocytes.[75,76] CAID has a multifactorial pathogenesis, which includes continuous immune system stimulation by microbial- and damage-associated molecular patterns (MAMPs, DAMPs), decreased hepatic synthesis of trophic factors and hypersplenism and the

etiological factors of cirrhosis such as alcohol or virus. Furthermore, the continuous interaction of gut microbiota with stimulation of the immune system may lead to exhaustion of the immune response and 'immune paralysis', which might further increase the risk of bacterial infections (Jalan et al, 2012).[77]

ROLE OF PPIs and NSBBs:

Several studies like the retrospective case-control study by Bajaj JS et al in 70 patients have found an association between the use of Proton pump inhibitors (PPIs) with SBP and *C. difficile*.[78] This is particularly important, as PPIs are some of the prescribed drugs in cirrhosis.[79] PPIs reduce gastric hydrochloric acid (HCl) secretion and predispose to small intestinal bacterial overgrowth, which is mostly the first step in the pathogenesis of most infections in cirrhosis.[80] A recent conundrum that has arisen is the association of non-selective β blockers (NSBBs) with negative outcomes in cirrhosis. While a meta-analysis showed a reduced development of SBP with NSBB use (Senzolo et al, 2009), a recent non-randomised study demonstrated worse survival in those who took NSBB with refractory ascites (Serste et al, 2010).[81,82] This deleterious effect of NSBBs on cirrhosis outcomes has led to the formulation of a 'window hypothesis', which suggests that NSBBs only improve outcomes in a narrow window of the cirrhosis' natural history.

RISK FACTORS OF SPECIFIC INFECTIONS IN CIRRHOSIS:

In the past, Gram negative bacteria had been isolated from more than 70% of culture positive bacterial infections.[51] However more recently from studies like the 12 year prospective study by Reuken et al in patients with cirrhosis, it has been seen that bacterial infections by Gram-positive cocci have increased in tertiary centers and now represent 60% of nosocomial culture-positive infections including spontaneous

bacteremia and SBP.[52,84] This shift has been attributed to the widespread, indiscriminate use of antibiotics leading to intestinal dysbiosis favoring Gram-positive BT.[85] An increased number of invasive procedures has also lead to increased Gram positive bacteremia with secondary organ spread.[52] Although translocation of gut microbial flora into the bloodstream is likely to occur during endoscopy because of mucosal trauma related to the procedure itself,[86] risk of bacteremia associated with endoscopic procedures is poorly investigated in non-bleeding cirrhotic patients. One study by Llach et al in 1999 reported an incidence of bacteremia of 10% after colonoscopy, but all cirrhotic patients with bacteremia remained asymptomatic.[87] Therefore there are no recommendations for routine antibiotic prophylaxis for cirrhotic patients undergoing colonoscopy[88] and it is advised that clinicians should decide on an individual case basis.[89]

Gastrointestinal (GI) bleeding is an important risk factor for infections in cirrhosis because bleeding facilitates pathological BT and infections. Infections, on the other hand, are associated with a higher rate of recurrent bleeding.[90] Antibiotic prophylaxis over seven days on cirrhotic patients in with gastrointestinal bleeding is the current standard of care [EASL (The European association for the study of the liver) clinical practice guidelines, 2010].[91] In a Cochrane review by Chavez-Tapia et al of nine controlled trials including 987 patients, the pooled incidence of bacteremia following GI bleeding was 15% without antibiotic prophylaxis and 3% with antibiotic prophylaxis, indicating a risk reduction of 75% with antibiotic prophylaxis.[91] Results favoring antibiotic prophylaxis were also obtained when other infections like SBP, pneumonia, urinary tract infection and the resultant mortality were studied.[92,93]

Patients with low ascitic fluid (AF) protein, severe liver failure, renal failure and low platelets are at the highest risk of developing community-acquired SBP

(Guarner et al, 1999).[94] SBP also having recurrence rate of 70% within the first year after the first episode.[95] Hence it is recommended to start antibiotic prophylaxis for the following high risk groups (from the position statement of the EASL special conference on bacterial infections in cirrhosis)[57]; Patients with low protein ascites (10–15 g/L), advanced liver failure (serum bilirubin >3.2 mg/dl, Child-Pugh class C) and low platelet count (<98,000/ cu. mm), impaired renal function (serum creatinine >1.2 mg/dl, BUN >25 mg/dl or serum sodium <130 mEq/L), history of GI bleeding, hepatic encephalopathy.[11,28,96-8] Patients with polymorphisms in genes involved in the innate antimicrobial defense, such as *NOD2*, *TLR2* and *MCP-1*, have a higher life-time risk to develop SBP.[57-9,99,100] Environmental factors, which are modifiable, such as alcohol use[101] and indiscriminate use of PPIs play a role in the development of SBP. Intravenous catheters and procedures like transjugular intrahepatic porto-systemic shunt (TIPSS) have also been incriminated in some cases.[102]

There are very few studies analyzing the risk factors of extra-peritoneal bacterial infections. The majority of identified urinary pathogens are Gram-negative bacteria with *Escherichia coli* as the most commonly isolated microorganism still, but multi-drug resistant bacteria are increasingly observed. According to a retrospective study by Reuken et al in 400 patients, the risk of UTI increases with age rather than with the severity of liver disease in contrast to other bacterial infections in cirrhosis.[103] As in patients without liver disease, reduction of unnecessary urinary catheter use applies.[104] Lower respiratory tract infections and pneumonia are associated with the highest risk of mortality in cirrhosis (Hung et al, 2013).[105] It has been demonstrated that low serum complement levels in rats with decompensated cirrhosis increase susceptibility to *Streptococcus pneumoniae*.[106] Since *S. pneumoniae* represents the most common etiologic agent isolated in community-acquired pneumonia,

pneumococcal vaccination with the 23-valent vaccine is recommended as a preventive measure in cirrhotics.[107,108] Walking barefoot has been identified as a risk factor for cellulitis in patients with cirrhosis and edema in an Indian study by Mohan et al (2011) and should be avoided.[109]

CONSEQUENCES OF BACTERIAL INFECTIONS:

While some patients with cirrhosis and acute bacterial infections have ‘‘mere’’ decompensated cirrhosis, others develop new acute liver dysfunction and/or extra-hepatic organ failures.[110] Patients with cirrhosis and these acute organ failures are at high risk of short-term death.[77,111] These patients are considered to have acute-on-chronic liver failure (ACLF).[77] The diagnostic criteria of ACLF have been defined by the CANONIC study (Moreau et al, 2013). This study used the CLIF (Chronic liver failure)-Sequential Organ Failure Assessment (SOFA) score to recognize organ failures.[5] The CANONIC study provided a robust definition of ACLF into three ACLF grades, with progressively increasing mortality risk (22% in grade 1 to 77% in grade 3).[5] Bacterial infections now common causes of ACLF (33%).[5]

Several mechanisms have been suggested for ACLF.

1) Bacterial components like lipopolysaccharide (LPS) cause an excessive pro-inflammatory response of the immune system resulting in tissue damage and organ failure.[112] It has been found in studies by Tazi et al and Thabut et al (2007) that the susceptibility to LPS-induced liver damege is higher in animals with cirrhosis than in normal animals.[113,114]

2) Infection-induced tissue damage also depends on the intrinsic capacity of host organs to tolerate the effects of the inflammatory response.[112] In contrast to a normal liver, cirrhotic livers are abnormally susceptible to LPS-induced, TNF-

α-mediated apoptosis because NFκβ-target anti-apoptotic molecules cannot be induced properly.[113]

3) Renal failure: Patients with SBP with no shock who exhibit high pro-inflammatory response are at risk of developing renal failure.[115] Renal failure in these patients frequently develops during resolution of infection suggesting organ failure does not result from intrinsic virulence but rather extrinsic virulence i.e. caused by the excessive inflammatory response of the host or sepsis-related alterations in hemodynamics (Sort et al, 1999).[116] The markedly reduced renal blood flow in decompensated cirrhosis[117] renders the kidney susceptible to infection-induced renal failure and hepatorenal syndrome (HRS).[118] Given the impact of renal failure on mortality in cirrhosis, current strategies implement the criteria of the Acute Kidney Injury Network (AKIN) (creatinine increase $\geq$ 0.3 mg/dL) within 48 h or 50% creatinine increase from a stable baseline, for all acute deteriorations of renal function in cirrhosis under the term "hepatorenal dysfunction" (Belcher at al, 2013).[119]

4) Brain failure: Bacterial infections are common triggers of hepatic encephalopathy.[120] Data from a study by Chavarria et al in 2013 which studied MRI brain changes in a rat model show that infections may result in brain edema, both intracellular and extracellular, in patients with cirrhosis.[121]

5) Disseminated intravascular coagulation (DIC): DIC is more frequent in patients with ACLF than in those without. Thrombi in the microvasculature of a vital organ may play a role in tissue hypoxia. Activation of coagulation factors may stimulate tissue inflammation.[112]

7) Circulatory dysfunction: Cirrhosis is associated with systemic circulatory dysfunction which is characterized by arterial splanchnic vasodilation, which progresses in parallel with the degree of liver impairment.[124] This is counter-acted initially by an increase in cardiac output, which is later negated by the diastolic dysfunction in cirrhotic cardiomyopathy.[125] Infection in cirrhosis is characterized by an intense inflammatory response with very high levels of cytokines[118] which exacerbate the underlying circulatory dysfunction.[126] Infection in a patient with baseline circulatory dysfunction can lead to acute renal failure, cardiac impairment, hepatic encephalopathy, type-1 hepatorenal syndrome and death.[127]

8) Endothelial dysfunction: The recognized markers of endothelial dysfunction are von Willebrand factor (vWF), P-selectin and isoprostanes. Endothelial dysfunction and higher levels of vWF, have been associated with a higher incidence of ACLF and higher mortality rates.[128,129]

DIAGNOSIS:

The EASL special conference held in 2013 concluded that all hospitalized patients with cirrhosis should be considered as potentially infected until proven otherwise.[57] Since bacterial infections in cirrhosis lead to rapid development of sepsis, multiple organ failure and death,[130] early diagnosis and treatment are of paramount importance. Bacterial infections in cirrhosis can be asymptomatic and have to be suspected in any cirrhotic patient with a sudden impairment of liver function.[22] Patients evaluated thoroughly including vital signs (temperature, respiratory and heart rates, mean arterial pressure), abdominal and chest examination, and presence of skin lesions. A review by Fernandez and Gustot in 2012 recommended that a complete work-up including complete blood cell count and culture, urinary sediment and culture, chest

X-ray, sputum culture, ascitic/pleural fluid cultures and abdominal ultrasonography should be done in all cases.[28]

SPONTANEOUS BACTERIAL PERITONITIS (SBP):

SBP is defined as an infection of the ascitic fluid in the non presence of a contagious cause of infection like intestinal perforation or abscess.[131] It has an incidence in hospitalized patients with cirrhosis of 7%-25%. Although there are no symptoms and signs in most patients[132], abdominal pain and fever are the most common symptoms, followed by vomiting, hepatic encephalopathy, gastrointestinal bleeding and renal dysfunction. The organism responsible for SBP is isolated in ascitic fluid or blood cultures in 40-60% of cases.[10,11,13,133] Diagnostic paracentesis should be done in all cases and at least 10mL of ascitic fluid should be inoculated into the blood culture bottle (Wiest et al, 2012).[14] Diagnosis of SBP is based on the demonstration of an absolute number of polymorphonuclear (PMN) cells in ascetic fluid $\geq$ 250/cu.mm. This warrants urgent initiation of a antibiotic therapy and must not be delayed until the results of the culture are available[131,134] (more specific with PMN count $\geq$500/mm^3 [135,136]). It is unclear whether a positive culture in the absence of elevated ascitic fluid PMN count (non-neutrocytic bacterascites), requires antibiotic therapy. In such a scenario, some guidelines recommend antibiotic treatment only if the patient shows signs of infection (Runyon BA, 2009).[134] Leucocyte reagent strips might help in bedside evaluation.[137,138] In patients with hemorrhagic ascites (red blood cell count > 10,000/cu.mm), subtraction of one PMN per 250 red blood cells should be made. A study by Parsi et al in 2008 suggested lactoferrin, an iron-binding protein contained in PMN, with a sensitivity of 96% and a specificity of 97% with cut-off value of $\geq$242 ng/mL in ascitic fluid as potential diagnostic marker for this SBP.[139] The most frequent causative organisms in community-acquired SBP are Gram-

negative bacteria, while in nosocomial infections, Gram-positive organisms are responsible. Secondary peritonitis is the main differential diagnosis of SBP, accounting for 5%-10% of all peritonitis in patients with cirrhosis and ascites. This is due to perforation or inflammation of an intra-abdominal organ, with a much higher mortality than SBP.[140] More than one bacteria can be grown on culture.[141] Secondary peritonitis is suspected when at least two of the Runyon's criteria are present: glucose <50 mg/dL; protein concentration >10 g/L; or lactate dehydrogenase >225 mU/mL. When secondary peritonitis is suspected, an urgent abdominal computerized tomography should be performed.[142]

URINARY TRACT INFECTION:

Urinary tract infections (UTI) in cirrhosis are mostly asymptomatic or oligosymptomatic.[143,144] Diagnosis is made on the basis of clinical suspicion in patients with fever, dysuria, frequency and urgency of micturition, urinalysis with leucocytes >10/hpf (high power field) and/or positive urine cultures $>10^5$ CFU/mm^3 [Bajaj JS et al, the North American consortium for the study of end-stage liver disease (NACSELD), 2012].[145]

PNEUMONIA:

Community- acquired pneumonia is most frequent, especially in subjects with active alcoholism.[146] Streptococcus pneumonia is the common causative organism, followed by *anaerobic bacteria* or *Haemophilus influenza*, *K. pneumonia*, *Mycoplasma pneumonia* or *Legionella.*[147] Factors such as tracheal intubation and hepatic encephalopathy may predispose for hospital acquired pneumonia, mainly caused by gram-negative bacilli and also by staphylococci.

BACTEREMIA:

Bacteremia without particular organ-specific source has been increasingly common in cirrhosis and can be divided into 2 entities (1) primary or spontaneous bacteremia and (2) secondary bacteremia. True primary bacteremia has the same initial step of pathogenesis as SBP, whereby bacteria flora in the gut lumen translocate.[84] Secondary bacteremia occurs when pathogens come from an exogenous source such as gastrointestinal bleeding, wound exposure and food-borne, or in healthcare-associated settings, such as transarterial chemoembolization,[148] transjugular intrahepatic portosystemic shunt,[149] therapeutic endoscopy[86] and intravenous catheters. The causative organisms are largely dependent on the origin of bacteremia. Diagnosis is made only after a blood culture positivity is acquired.[150]

SPONTANEOUS BACTERIAL EMPYEMA:

Spontaneous bacterial empyema (SBEM) is the infection of a pre-existing hydrothorax in which pneumonia has been excluded. It is present in 10-20% cases of hepatic hydrothorax.[151,152] Pathogenesis is similar to SBP.[153] The criteria for diagnosis are:(1) pleural fluid polymorphonuclear neutrophil (PMN)≥ 250 cell/mm ^{3} with a positive culture or≥ 500 cells/mm ^{3} with a negative culture; and (2) exclusion of a parapneumonic effusion (Xiol et al, 1996 and Alonso et al, 2010).[151,153] Culture of pleural fluid should be performed by inoculating 10 mL of pleural fluid into a blood culture bottle at bedside, which is the same as the standard recommendation for SBP.[153] A repeat thoracocentesis can be done in resistant cases but chest tube drainage is contraindicated.[153]

CELLULITIS:

Gram-stained smears from pus and/or infected tissue should be immediately obtained and broad-spectrum antibiotics should be prompt utilized because of the high morbidity and wide range of bacteria causing skin and soft tissue infections (SSTI).[150] Necrotizing fasciitis in cirrhotic patients sometimes develops without an obvious portal of entry in the extremities, thereby suggesting a potential alternative pathway of bacterial translocation and bacteremia leading to the SSTI.[154,155] The common causative organisms are Gram-positive cocci (*S. aureus*, beta-hemolytic *streptococci*) and Gram-negative enteric bacteria (occasionally polymicrobial) but lately, the incidence of Gram-negative pathogens, such as *E. coli*, *Klebsiella spp. , Aeromonas spp., Vibrio spp*., has increased in cirrhotic patients.[156] Fragile, thin and edematous skin, poor hygiene standards, malnutrition, frequent hospitalization and invasive procedures are the risk factors for SSTI.

ENDOCARDITIS:

A recent review by Fernández Guerrero et al of 316 infectious endocarditis (IE) cases,classically occur in patients with valvular heart disease and prosthetic valve, found that approximately 10% of patients had underlying liver cirrhosis.[157] Since the majority of IE cases in cirrhosis were health-care associated, the incidence of drug-resistant pathogens is considerably increased.[157,158] Hence a minimum of 4-6 weeks antibiotics is required and treatment failure and mortality rates are very high.

MENINGITIS:

Incidence and virulence of bacterial meningitis have been substantially increased in cirrhotic patients[159]; thus, mortality rate in these patients is approximately 50%-63% and even higher in older patients and those with alcohol-related

cirrhosis.[160,161] In patients with fever with headache and/or alteration of consciousness in cirrhotic patients, the possibility of a central nervous system infection should not be overlooked. Neurological examination could be misleading because of the presence of concurrent hepatic encephalopathy.[150]

CLOSTRIDIUM DIFFICILE:

C. difficile infection have recently been recognized as a significant problem in hospitalized cirrhotic patients. The Nationwide Inpatient Sample (NIS) of over 80,000 patients suggested that *C. difficile*-associated diarrhea (CDAD) was an independent risk factor of death in cirrhotic patients (Bajaj JS et al, 2010).[162]

NEW METHODS FOR EARLY DETECTION OF INFECTIONS:

1) Markers of gut dysbiosis/bacterial translocation (BT):

In a prospective case-control study by Gundling et al, Calprotectin levels after variceal hemorrhage, were shown to correlate with BT.[163] Markers of BT such as endotoxin, D-lactate, peptidoglycan and bacterial DNA are elevated in the serum of patients with cirrhosis.[164,165] However, detection of bacterial DNA won't correlate with infection.[166]

2) Markers of innate immune response:

Neutrophil function is impaired in cirrhosis, displaying an inadequately increased resting oxidative burst with a defect in phagocytosis and killing.[167] Similar functional defects are seen with monocytes and macrophages. Whether they can be used as indicators of susceptibility to infection needs to be tested.[168]

3) Markers of inflammatory response:

Although there was evidence that serum levels of these acute-phase proteins are not significantly lower in patients with cirrhosis than in other patients,[169] patients with cirrhosis may present reduced C-reactive protein (CRP) and procalcitonin (PCT) levels.[170] The predictive power of CRP and PCT for detecting infection had been found to be the similar in patients with and also without cirrhosis.[171,172] Role of other acute phase proteins (lipopolysaccharide binding protein, sCD14) in the early diagnosis in patients with cirrhosis is still unclear.[173] In a 2012 study by Reuken PA et al, mid-regional pro-adrenomedullin (MR-proADM) has been shown to provide more valuable information in infected patients with cirrhosis compared to CRP.[174]

4) New tools for early identification of the pathogen:

Real time polymerase chain reaction (PCR) assays[96,175] have been shown to have comparable utility to standard culture techniques for the diagnosis of SBP in cirrhosis.[176] As they are expensive and time-consuming and they need special equipment and technical expertise for DNA extraction, they may not be suitable as a replacement of cultures for routine use in clinical practice. A study by Espinal et al in 2012 has shown the the application of direct susceptibility testing (DST) based on a Matrix Assisted Laser Desorption Ionization – Time of Flight (MALDI-TOF) from positive blood cultures for early detection of resistant bacteria and their antibiotic susceptibility.[177]

MANAGEMENT OF BACTERIAL INFECTIONS IN CIRRHOSIS

SPONTANEOUS BACTERIAL PERITONITIS:

Third generation cephalosporins are the standard treatment of SBP.[178-80] The organisms commonly associated with community acquired SBP are Gram-negative bacteria, mainly *Enterobacteriaceae*. Intravenous cefotaxime 2g/q12h is considered the first-line antibiotic for the empirical treatment of SBP. Other effective and safe options are IV ceftriaxone 1g/q(12-24)h or IV amoxicillin-clavulanic acid (1-2)g/ q(6-8)h.[181] A reduction in the ascitic fluid PMN count < 25%, compared with the pretreatment value, after 2 days of antibiotic treatment[131] is considered treatment failure and indicates the need for modification of the antibiotic treatment according to sensitivity.[17] A 2-yr retrospective study by Piroth et al reported an increasing prevalence of extended-spectrum β-lactamase (ESBL)-producing bacteria and multi-resistant Gram-positive bacteria such as *Enteroccocus faecium* or multidrug resistant *Staphylococcus aureus* (MRSA).[182]

In fact, bacteria isolated in nosocomial SBP are frequently resistant to β-lactams (33%-78%), and this is frequently associated with treatment failure.[183.184] Carbapenems are the most effective option for nosocomial infections in areas with a high prevalence of ESBL- *Enterobacteriaceae*. Penicillin used in combination with β-lactamase inhibitors (e.g., piperacillin-tazobactam) and tigecycline may be an adequate alternative.[185] The need for primary prophylaxis for SBP in high-risk groups and secondary prophylaxis with prior SBP with norfloxacin 400mg/d or Ciprofloxacin 500mg/d has already been mentioned (Table 1). The development of infections by quinolone-resistant organisms was the main complication of long-term norfloxacin prophylaxis.[133] A study by Ortiz et al showed that infections in cirrhotic patients on chronic quinolone prophylaxis was mostly due to Gram positive organisms (79%).

This study also showed the emergence of severe nosocomial *Staphylococcal* infections due to methicillin-resistant strains. Therefore, SBP prophylaxis should be considered only in high-risk populations or the patients awaiting liver transplantation.[186]

ROLE OF IV ALBUMIN:

Administration of albumin as adjuvant treatment to antibiotics, at a dose of 1.5 g/kg on day 1 and 1 g/kg on day 3 was considered essential in patients with SBP and impaired renal or liver function, in order to prevent worsening of renal function.[127,187,188] The concomitant use of albumin decreased the incidence of type 1 hepatorenal syndrome (from 30% to 10%) and reduces mortality (from 29% to 10%), compared with cefotaxime alone (Sort et al, 1999).[116] This is particularly effective in patients with serum bilirubin ≥4 mg/dL or serum creatinine ≥1 mg/dL. [189] The mechanism involved could be related to its oncotic properties but also to its immunomodulation, antioxidant and endothelium stabilization capacity.[190]

MANAGEMENT OF SEPSIS AND SEPTIC SHOCK:

A prompt (within the 6 first hours) resuscitation of sepsis-induced hypoperfusion with pre-defined targets (central venous pressure 8–12 mmHg, urine output >0.5 ml/kg/hr and superior vena cava or mixed venous saturation 70% or 65% respectively) and normalization of increased lactate levels was recommended (Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012).[194] Arterial pressure must be increased to a level close to the baseline of each patient, if known. If not known, it should be at least 65 mmHg. The balance between fluid therapy and vasopressor administration in the hemodynamic support of cirrhotic patients is undefined. A strict monitoring of patients'

responsiveness to fluid replacement (i.e., pulse pressure variation and stroke volume variation in sedated patients) is necessary to avoid fluid overload, peripheral edema and abdominal compartment syndrome. Current guidelines only recommend stress dose steroids with patients with vasopressor-unresponsive septic shock in the general population.[195] A large double-blind European randomized control trial (RCT) is currently underway to address this topic.[57]

INDICATION	**ANTIBIOTIC AND DOSE**
Gastrointestinal bleeding	Preserved liver function: norfloxacin 400 mg/12h PO for 7 days; Patients with advanced cirrhosis (at least 2 of the following: ascites, jaundice, hepatic encephalopathy and malnutrition): IV ceftriaxone 1 g/d during 7 days
Primary prophylaxis of SBP in patients with low protein ascites (<15 g/L)	Norfloxacin 400 mg/d PO or ciprofloxacin 500 mg/d until liver transplantation or death in patients with advanced cirrhosis: 1. Child-Pugh score ≥9 points with serum bilirubin ≥3 mg/dl and/or 2. Renal dysfunction (serum creatinine ≥1.2 mg/dl, BUN≥25 mg/dl and/or serum sodium ≤130 mEq/L)
Secondary prophylaxis of SBP	Norfloxacin 400 mg/d PO until liver transplantation, death, resolution of ascites or improvement in liver function to a compensated status

Table 1: CURRENT INDICATIONS FOR ANTIBIOTIC PROPHYLAXIS IN CIRRHOSIS.[94,131,191-3]

MULTI-RESISTANT (MR) BACTERIA- HOW TO TACKLE THIS BOMB?

Epidemiological studies (Fernandez et al, Tandon et al, 2012) have demonstrated that long-term norfloxacin prophylaxis has increased the prevalence of infections caused by quinolone-resistant, cotrimoxazole-resistant and ESBL-producing strains with cirrhosis.[12,196] Long-term norfloxacin prophylaxis increases 2.7 fold the risk of developing MR bacterial infections and almost 4 fold the risk of infections caused by ESBL-producing *Enterobacteriaceae*.[11,12,196] Rifaximin, an antibiotic with broad-spectrum antimicrobial activity that eliminates intestinal flora non-selectively[197], has been suggested as a potential alternative to norfloxacin. Its administration in patients with hepatic encephalopathy was not associated with the risk of development of infections by MR bacteria.[198] The advantages over norfloxacin accorded by rifaximin are[197,198]

Type of infection	Community acquired infections	Nosocomial infections
SBP, SBE and spontaneous bacteremia	Cefotaxime **or** ceftriaxone **or** amoxicillin/clavulanic acid	Piperacillin/tazobactam **or** meropenem **±** glycopeptide
Urinary infections	Uncomplicated: ciprofloxacin **or** cotrimoxazole If sepsis: cefotaxime **or** ceftriaxone **or** amoxicillin/clavulanic acid	Uncomplicated: nitrofurantoin **or** fosfomycin If sepsis: piperacillin/tazobactam **or** meropenem **±** glycopeptide
Pneumonia	Amoxicillin/clavulanic acid **or** ceftriaxone + macrolide **or** levofloxacin or moxifloxacin	Piperacillin/tazobactam **or** meropenem/ceftazidime + ciprofloxacin **±** glycopeptide should be added in patients with risk factors for MRSA
Cellulitis	Amoxicillin/clavulanic acid **or** ceftriaxone + oxacillin	Meropenem/ceftazidime + oxacillin **±** glycopeptide

Table 2: Recommended empirical antibiotic treatment for bacterial infections in cirrhosis.[28,131]

1. It reaches high fecal concentrations but was virtually non-absorbed (bioavailability in blood after oral administration <0.4%).

2. It reduces the expression of bacterial virulence factors and compromises plasmid transfer, an important mechanism of multiresistance.

3. Rifaximin produces minimal alterations in the intestinal microflora.

Non-antibiotic strategies[199-202] have been studied as a potential alternative to quinolones such as non-specific β-blockers, anti-oxidants, cisapride and probiotics. None of them have provided better results compared to norfloxacin in the prevention of SBP in an RCT in patients with cirrhosis.

AIMS AND OBJECTIVES

AIM

The prevalence of bacterial infections in patients with liver cirrhosis.

PRIMARY OBJECTIVES

To estimate the prevalence of bacterial infections in liver cirrhosis.

SECONDARY OBJECTIVES

To find out the association of bacterial infections in liver cirrhosis with various demographic and clinical factors like age, sex, gastrointestinal (GI) hemorrhage, Child Pugh class, H/o any invasive procedures, grade of ascites and encephalopathy and various laboratory parameters.

MATERIAL AND METHODS

STUDY PERIOD: January 2017 to June 2017.

SETTING AND STUDY SUBJECTS: The study was undertaken at Govt Kilpauk Medical College & Hospital, Kilpauk in the departments of Medicine and Microbiology. Subjects were recruited from Medical OPD, emergency and wards of the hospital.

TYPE OF STUDY: Descriptive, cross-sectional study

SAMPLE SIZE: Previous literature suggests infection rate of around 25-45%. So taking 35% as the infection rate with 10% precision either side, a sample size of 50 subjects would have been adequate (calculated using the formula $3.84*p*(1-p)/n^2$.

INCLUSION CRITERIA:

The participants in the study were patients diagnosed with liver cirrhosis on the basis of liver biopsy, or clinical evidence of decompensation or varices, and/or radiological evidence of nodularity of liver and collaterals in a patient with chonic liver disease[145].

EXCLUSION CRITERIA:

Patients who had received antibiotics in the past one week, DM, Immunocompromised patients

METHODS:

Informed consent was taken from all patients. A detailed history was taken and complete physical examination was done. Routine investigations like Complete blood count, Liver function tests, Kidney function tests, prothrombin time/INR, partial thromboplastin time were done in all patients. Patients of liver cirrhosis were classified into classes A, B, C based on Child Pugh classification (Table 3).

Clinical and lab criteria	**Points**		
	1	**2**	**3**
Encephalopathy	None	Grade 1/2	Grade 3/4
Ascites	None	Mild-moderate	Massive
Bilirubin (mg/dL)	<2.0	2.0-3.0	>3.0
S.Albumin (g/dL)	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3
Class A= 5-6 points **Class B= 7-9 points** **Class C= >9 points**			

Table 3: Child Pugh Classification

Patients were assessed for the presence of following infections, 1) Spontaneous bacteremia 2) Spontaneous bacterial peritonitis and its variants 3) Urinary tract infections 4) Lower respiratory tract infections 5) Skin infections 6) Other infections as indicated by the clinical picture.

All included patients were subjected to blood culture to look for spontaneous bacteremia, before antibiotics are started. Samples for blood culture were collected by venepuncture after cleaning the local area with alcohol swab. The rubber cap of the blood culture bottle was cleaned with an alcohol swab by circular motion. A

maximum of 10 mL blood was collected and inoculated in BacTec 9120 system (Becton Dickson). A positive reading indicated the presumptive presence of viable organisms.

Ascitic fluid biochemical and cytological examination was done in all patients as all patients in our study had some degree of ascites. Ascitic fluid collection was done using an 18 gauge needle attached to a 10mL syringe, after cleaning the local area with alcohol swab under aseptic precautions. Polymorphonuclear cells count was done by charging in the Neubauer chamber using a light microscope. 10mL of ascitic fluid was inoculated in BacTec blood culture bottles. A positive reading indicated the presumptive presence of viable organisms. Positive isolates were subcultured on blood agar and MacConkey agar plates. Standard biochemical tests were performed. Spontaneous bacterial peritonitis was defined as ascitic fluid polymorphonuclear cells >250/microlitre with a positive fluid culture; culture negative neutrocytic ascites by ascitic fluid polymorphonuclear cells >250/microlitre without positive fluid culture; monomicrobial non-neutrocytic bacterascites by positive ascitic fluid culture with ascitic fluid polymorphonuclear cells <250/microliter.

Lower respiratory tract infections was diagnosed based on the following criteria: new pulmonary infiltrate in the presence of a) at least one respiratory symptom (cough, sputum production, dyspnea, pleuritic pain) with b) at least one finding on auscultation (rales or crepitations) or one sign of infection (core body temperature >38^0C or <36^0C, shivering, leucocyte count >10,000 or <4000/cumm) in the absence of antibiotics[145]. If the above criteria were fulfilled, sputum culture was done. After following all instructions (no food should be ingested 1-2 hours prior to expectoration, mouth should be rinsed with water or normal saline, deep cough

expectoration) first morning sample was collected in wide mouth open sterile container, with an attempt to minimize contamination with saliva. It was transported to laboratory as soon as possible. Macroscopic and microscopic examination was done. Microscopic examination was done using Gram staining. Homogenisation was done using N-acteyl-L-cysteine. Decontamination will be done using 4% sodium hydroxide. Sample was inoculated on blood agar, MacConkey agar, and chocolate agar. Standard biochemical tests were done to identify the causative organisms.

Urinary tract infections was diagnosed by clinical signs and symptoms (dysuria, fever), urine WBCs >15/hpf and/or positive urine culture[22]. Early morning, mid-stream clean catch urine were collected. They were transported to the laboratory immediately. If there was a delay, samples were preserved at 4ºC. Macroscopic and microscopic examinations were done. Samples were inoculated on CLED (cysteine-lactose electrolyte deficient agar) media. On all positive growth plates, after Gram staining, standard biochemical tests were done to find out the causative organism.

Skin infection was diagnosed in case of, fever with cellulitis [local signs (blush, tumefaction, pain)], leucocytosis with neutrophilia, positive cultures of wound secretion][22]. Sample for culture were collected using sterile cotton swab, inserted into the depth of the lesion and transferred into a sterile container. Culture was done on appropriate nutrient agar, after incubation at 37º Celsius.

For other infections including spontaneous bacterial empyema and meningitis, appropriate samples were collected and cultures ordered.

The Kirby Bauer disc diffusion method was used to determine the susceptibilities to routinely used antibiotics and results were interpreted as per CLSI (Clinical Laboratory Standard Institution) guidelines.

Patients with infections were assessed for association with various demographic and clinical factors like age, gender, history of gastrointestinal haemorrhage (within 1 week of the study), invasive procedures like upper GI endoscopy, bladder catheterization (within 2 weeks of the study), grade of ascites and encephalopathy, vital signs like blood pressure, pulse rate, respiratory rate and axillary temperature, Child Pugh class and laboratory parameters like complete blood count, liver function tests, kidney function tests, PT/INR and ascitic fluid protein.

STATISTICAL ANALYSIS

- Data will be entered into Microsoft Excel.
- Simple frequency distribution tables were generated and normally distributed variables were summarized as mean and standard deviation.
- Prevalence of all bacterial infections and specific infections were calculated as a percentage.
- Chi-square test/Fisher's exact test was used to study the association of bacterial infections with dichotomous / polytomous variables.
- Unpaired t test was used to see the association of bacterial infections with continuous variables.
- $P < 0.05$ was considered as significant.
- Chi-square test for trends was used to assess the trend of infections with polytomous ordinal variables.

Fig. 1: Age distribution

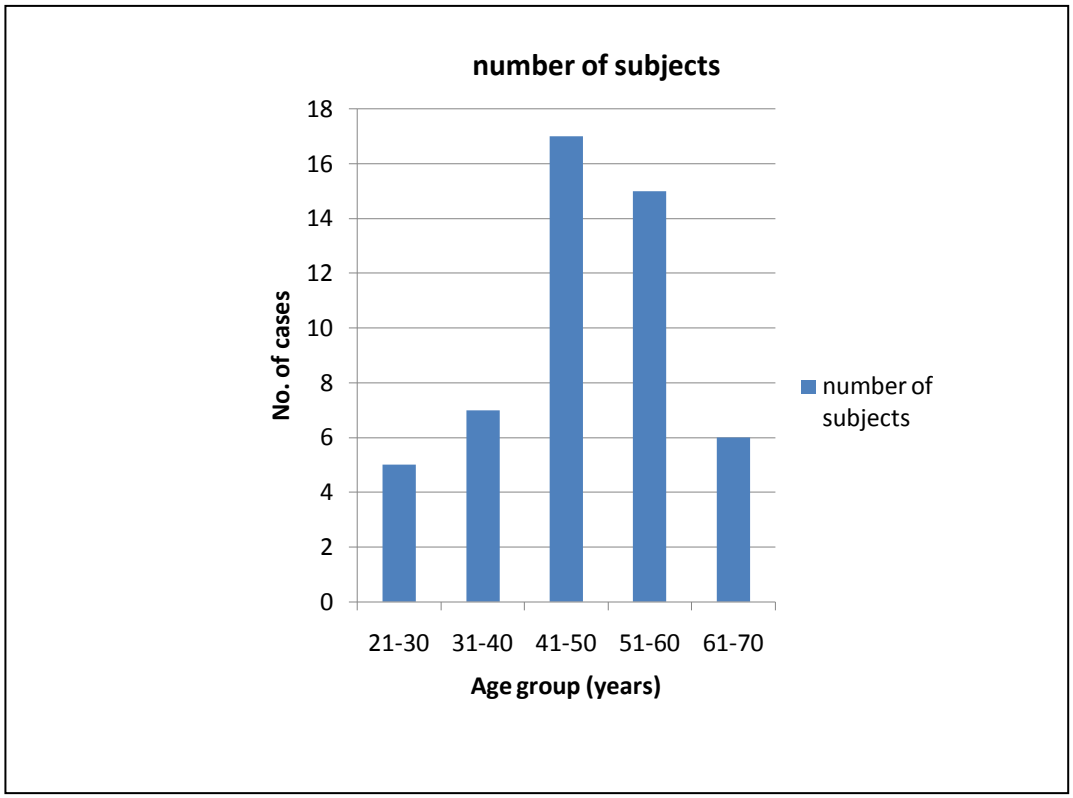


Fig. 2: Gender distribution

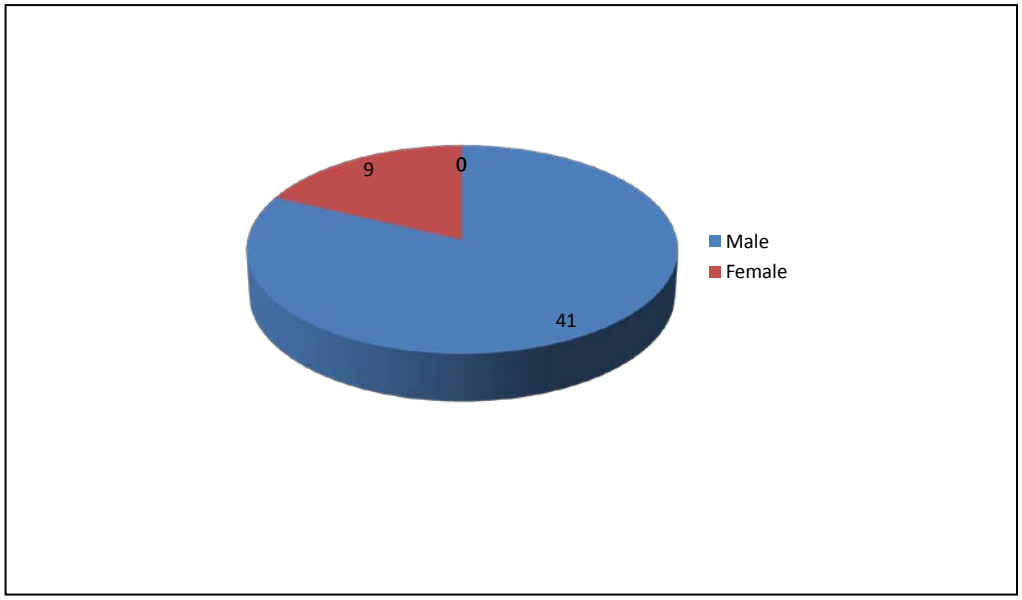


Fig. 3: History of GI Hemorrhage

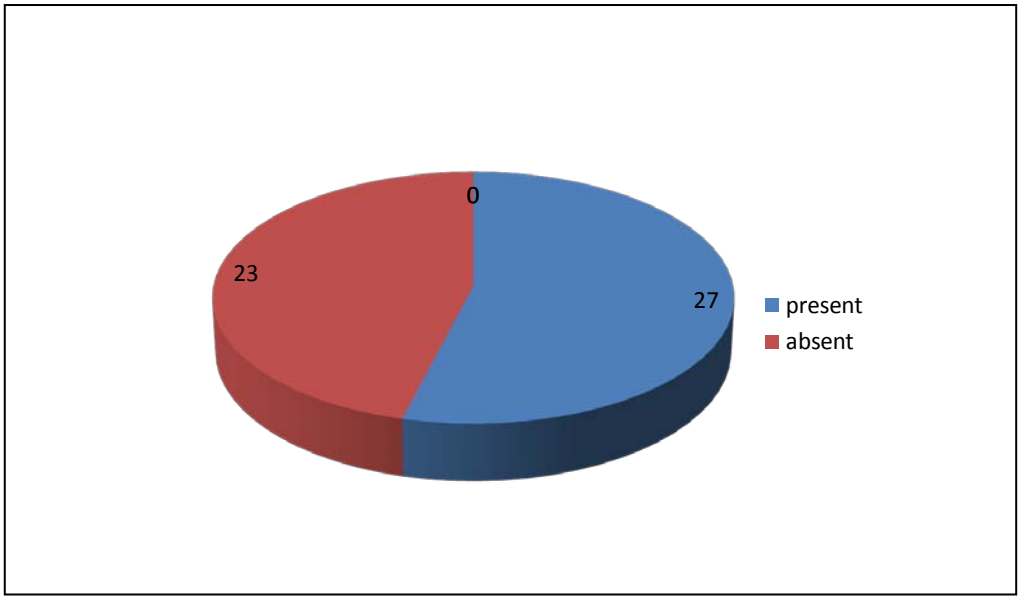


Fig. 4: History of invasive procedures

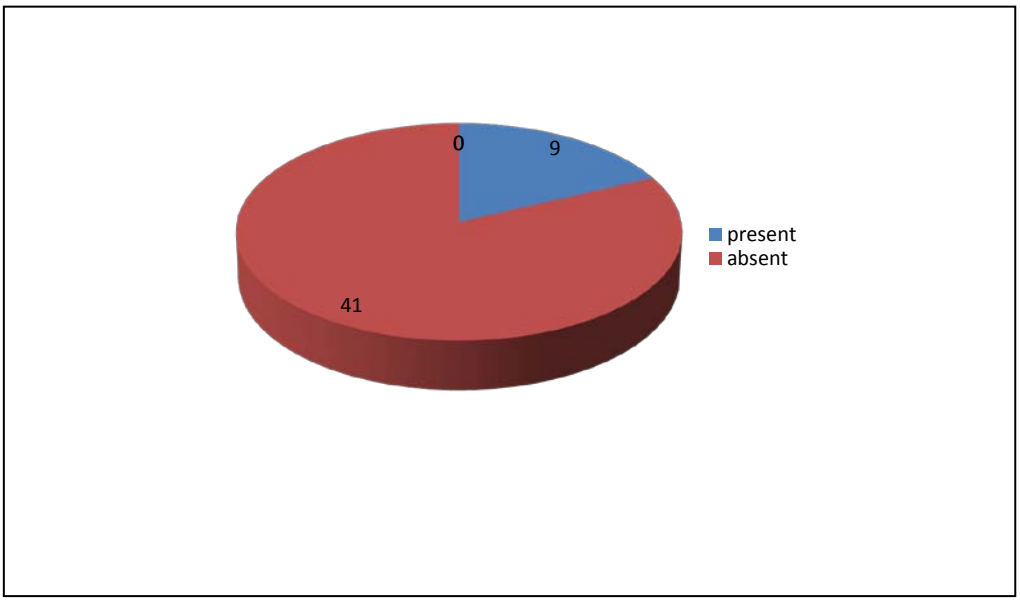


Fig. 5: Etiology of cirrhosis

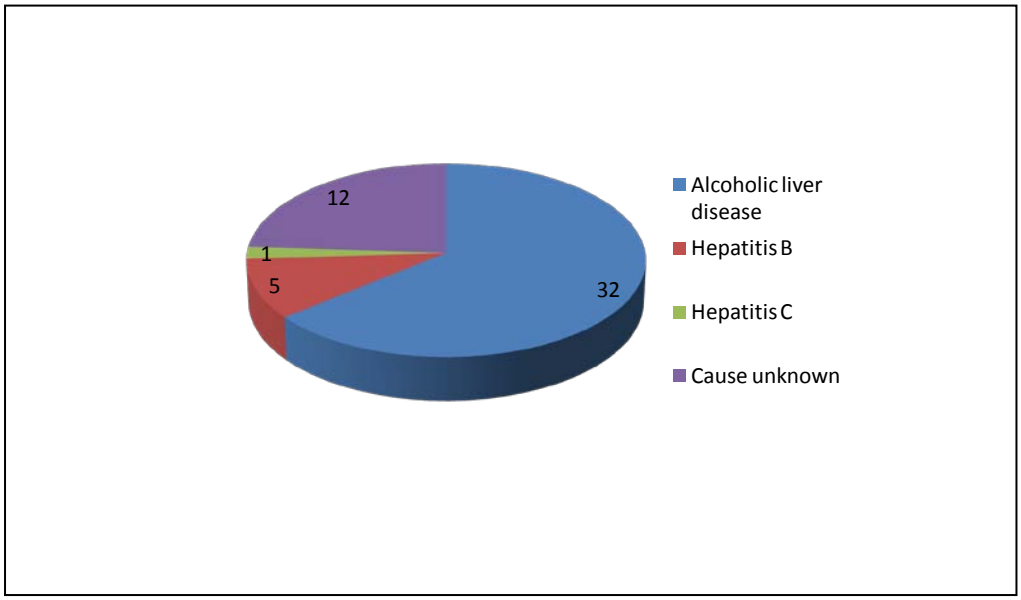


Fig. 6: Systolic Blood Pressure (mmHg)

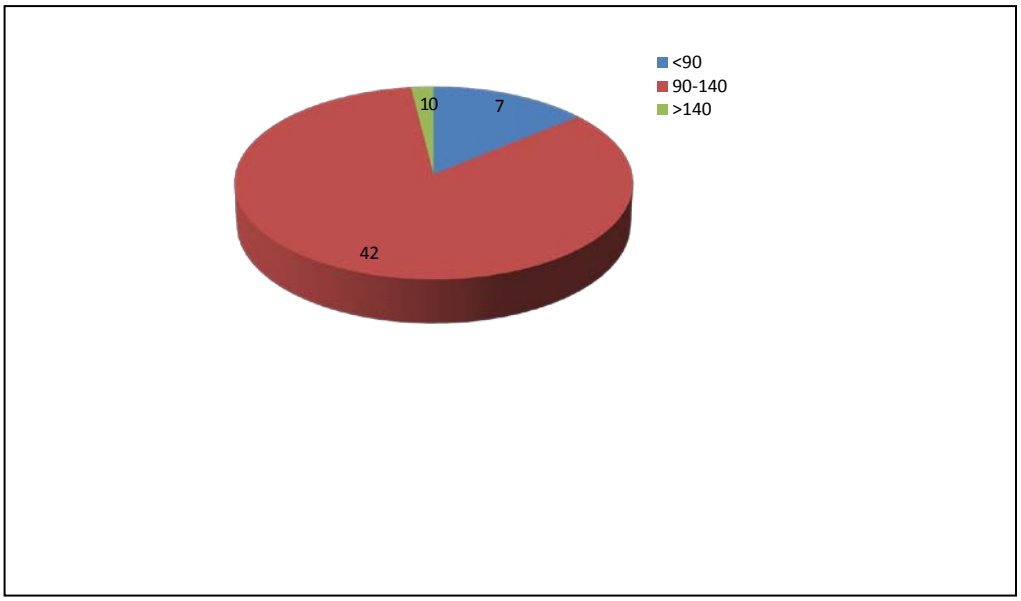


Fig. 7: Grading of ascites

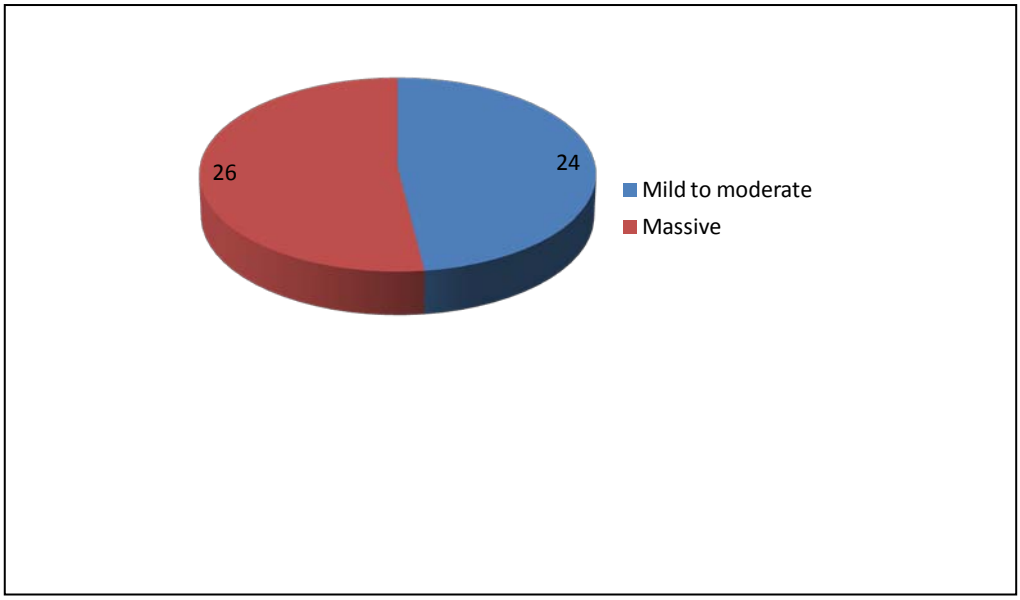


Fig. 8: Grading of encephalopathy

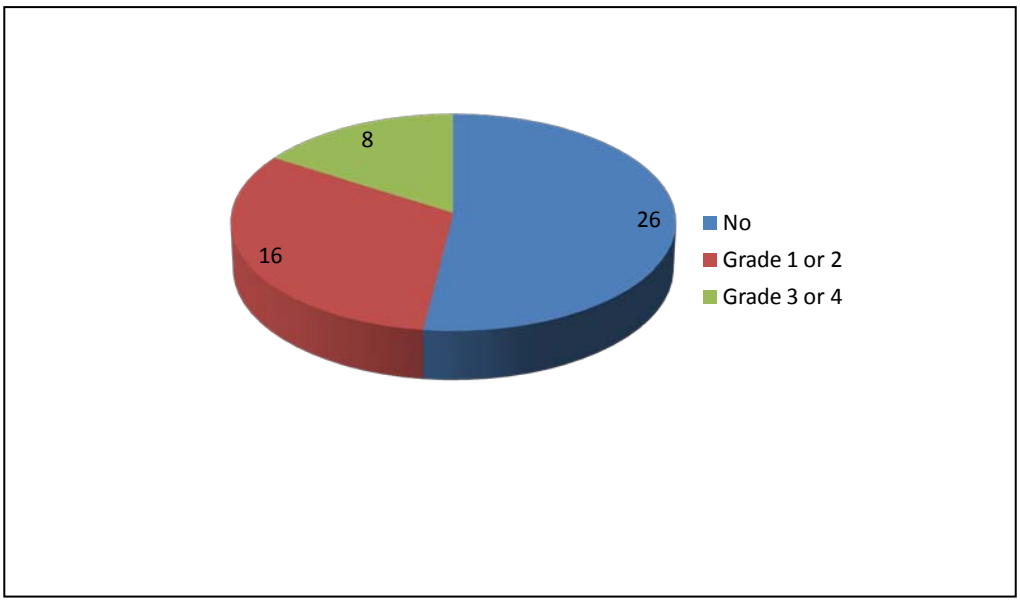


Fig. 9: Child Pugh classes

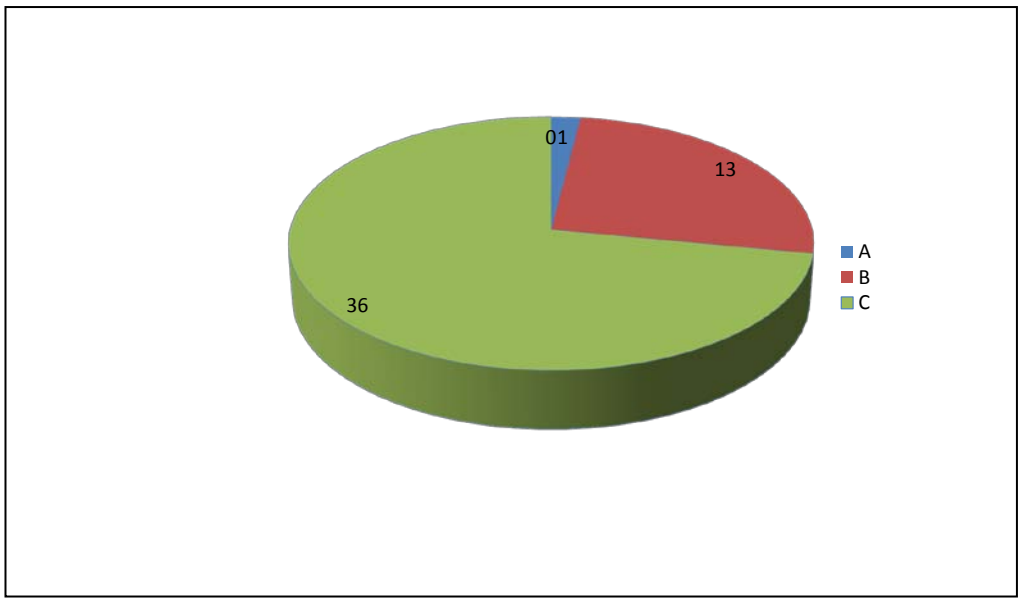


Fig. 10: Prevalence of different infections

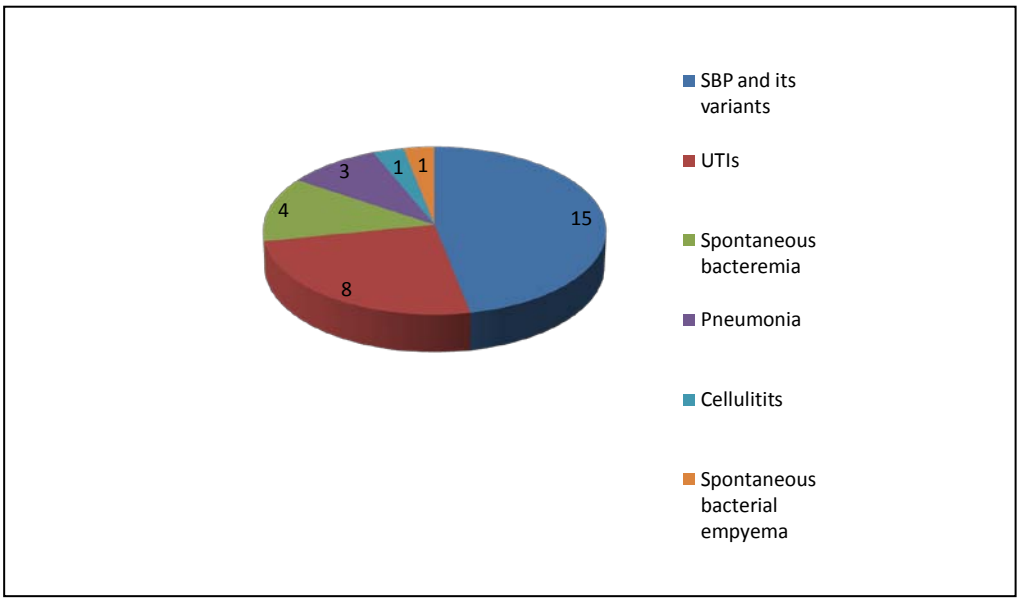


Fig. 11:Organisms grown on culture

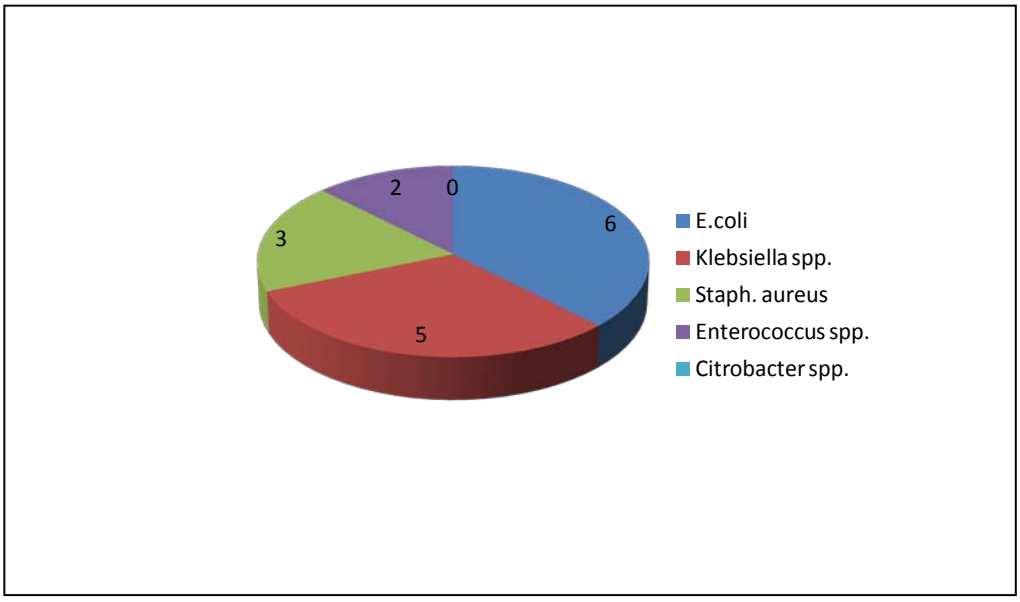


Fig. 12: Correlation with gender

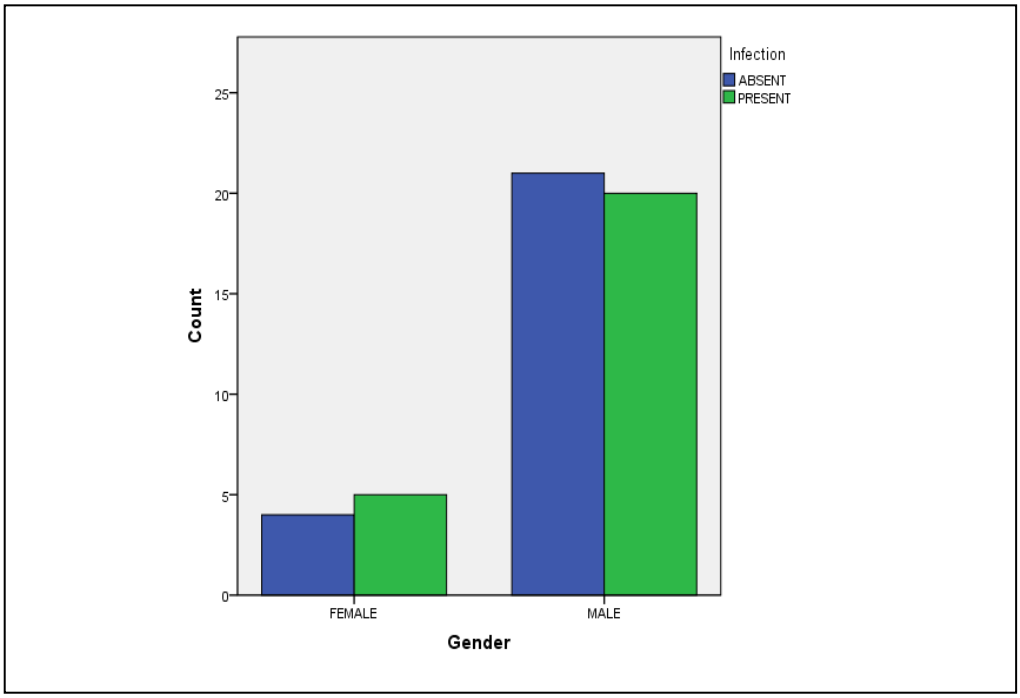


Fig. 13: Correlation with GI hemorrhage

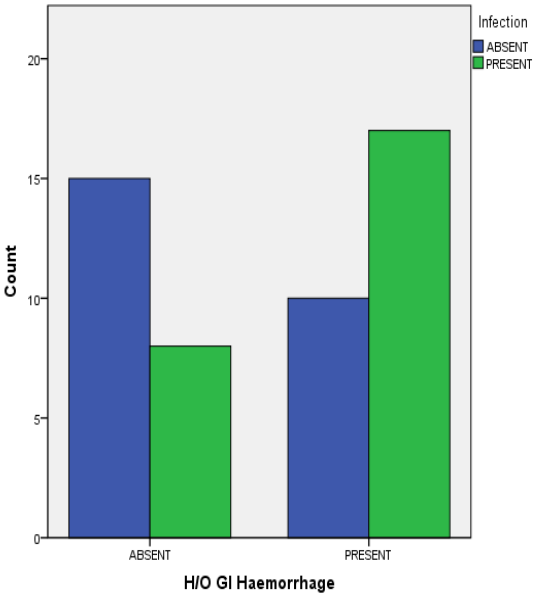


Fig. 14: Correlation with invasive procedures

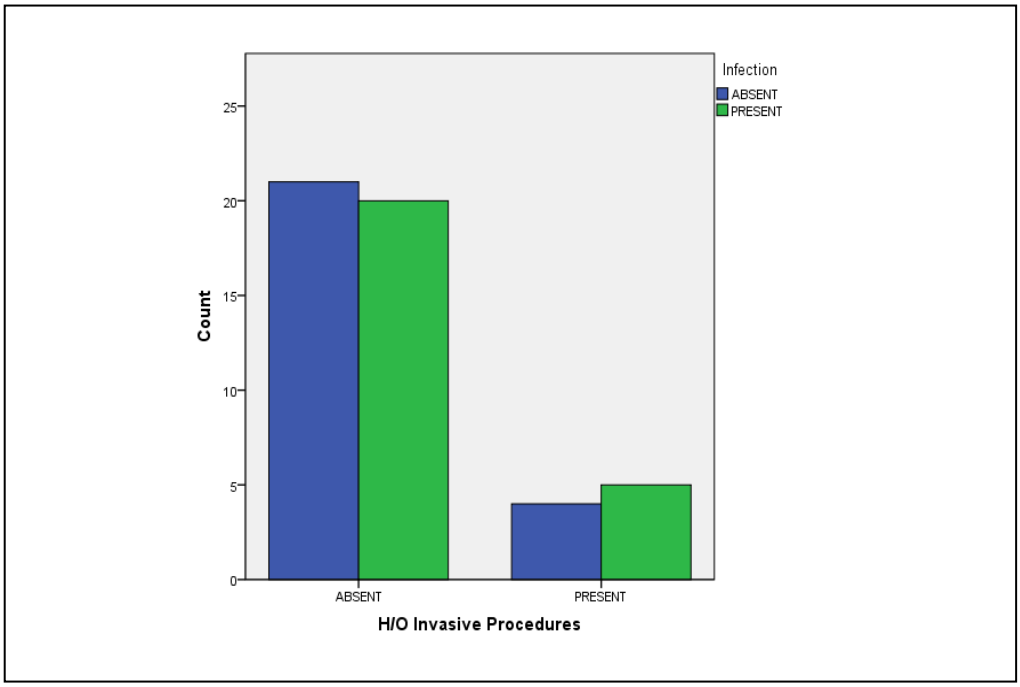


Fig. 15: Correlation with systolic BP

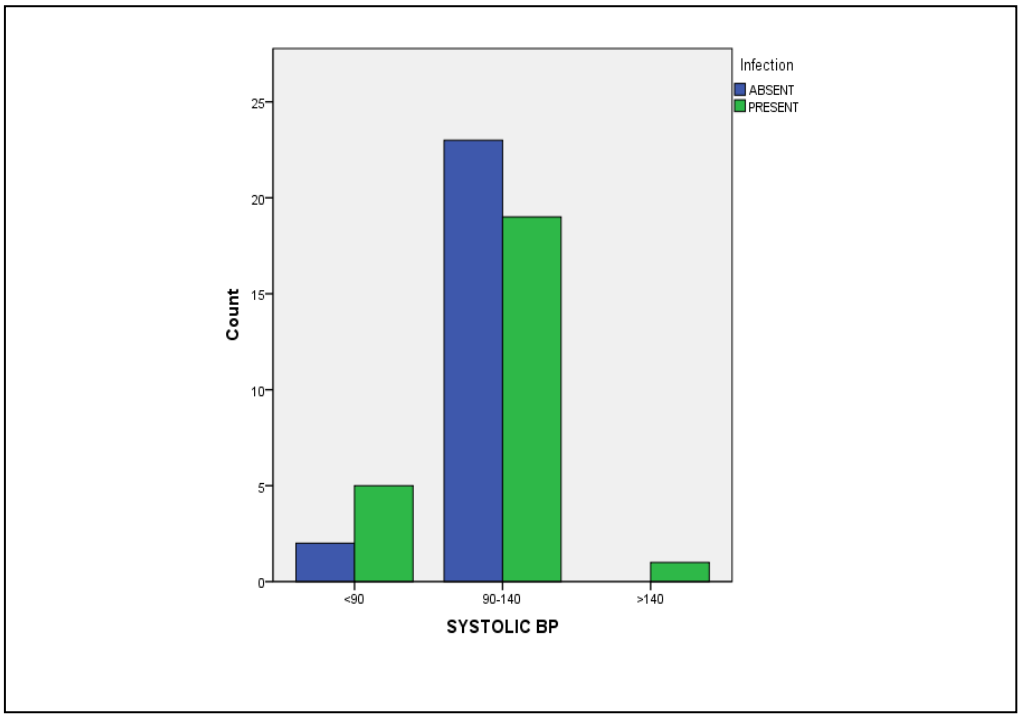


Fig. 16: Correlation with pulse rate

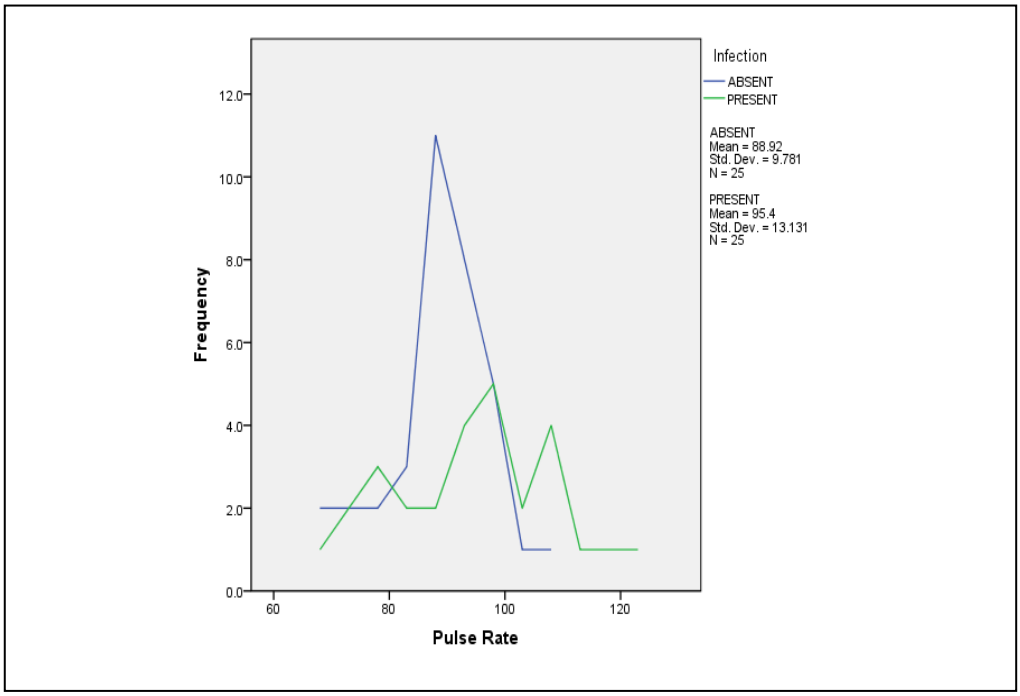


Fig. 17: Correlation with respiratory rate

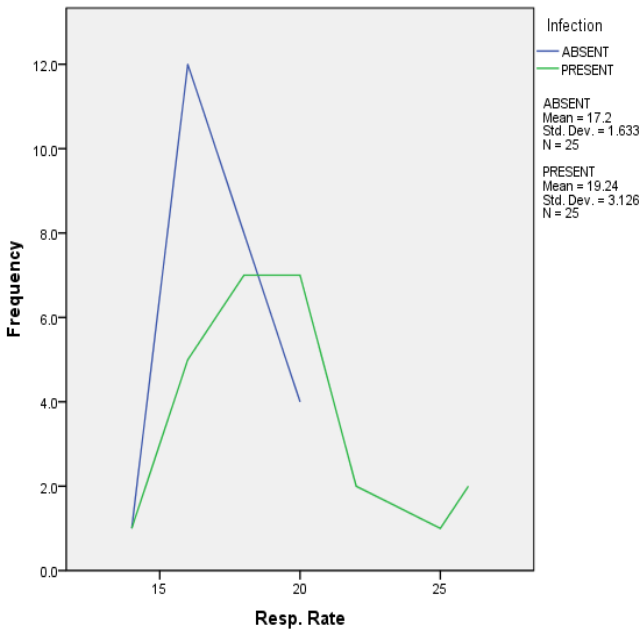


Fig. 18: Correlation with axillary temperature

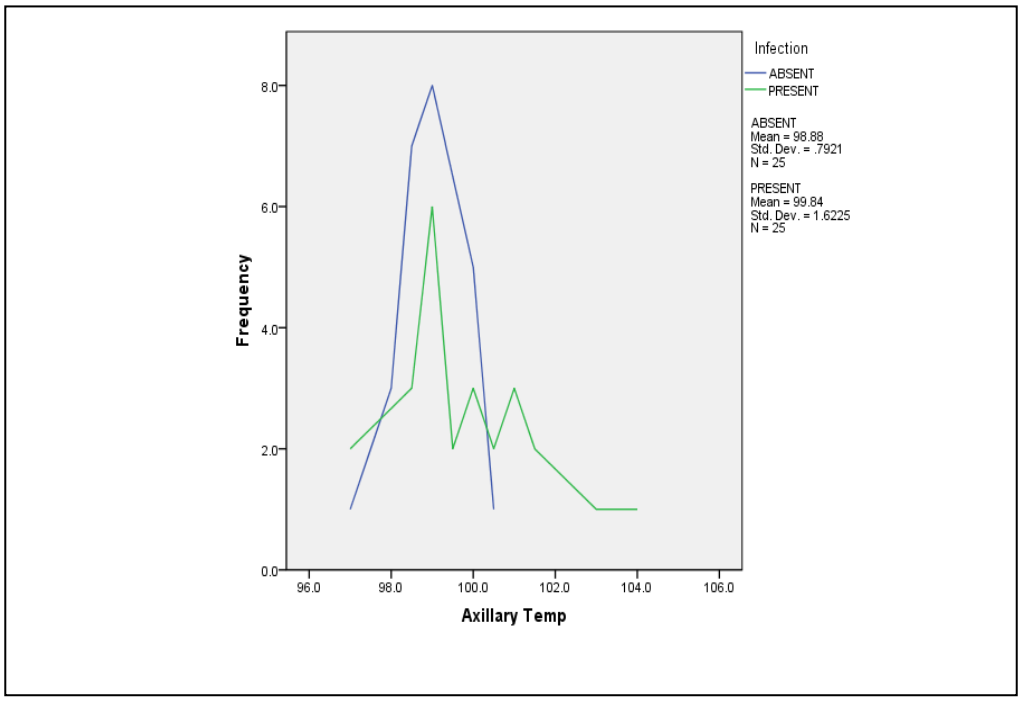


Fig. 19: Correlation with platelet count

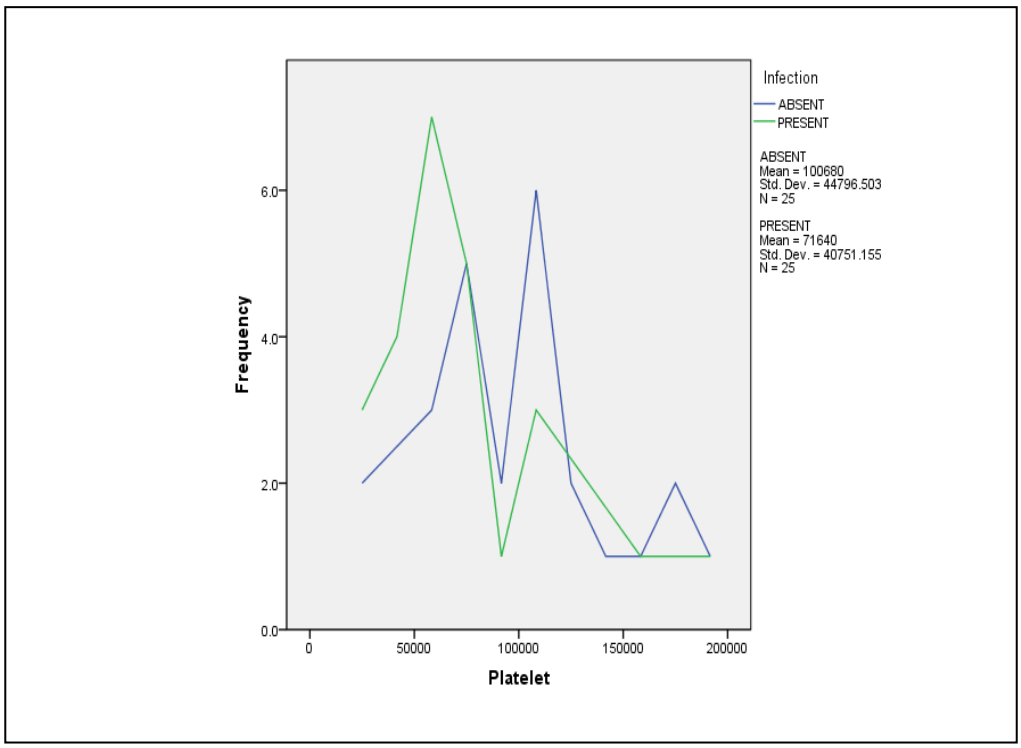


Fig. 20: Correlation with serum total protein

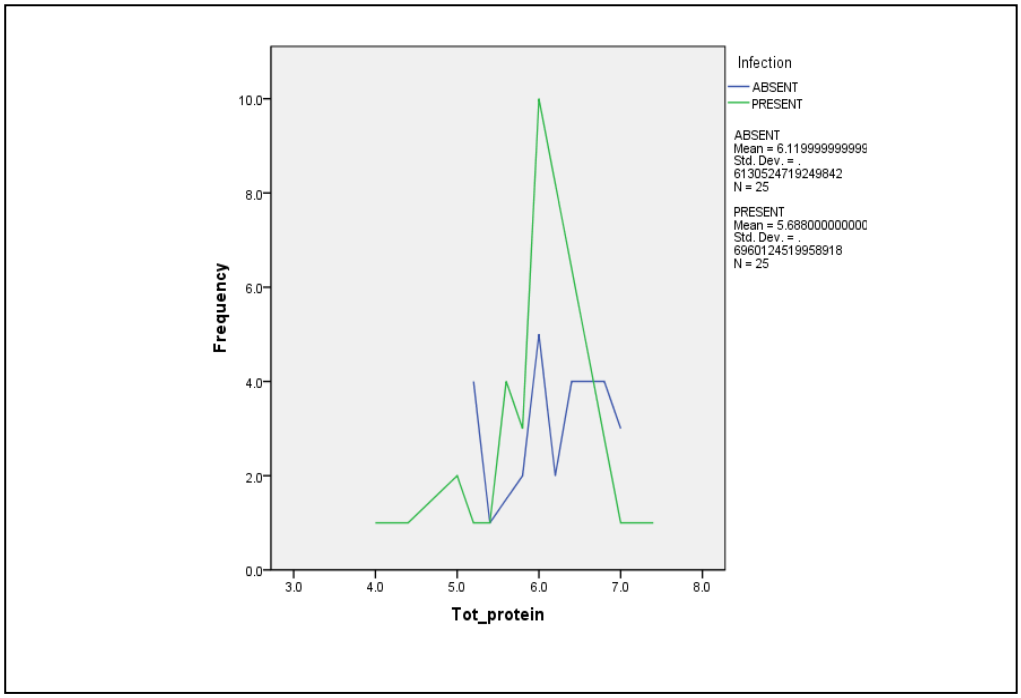


Fig. 21: Correlation with serum albumin

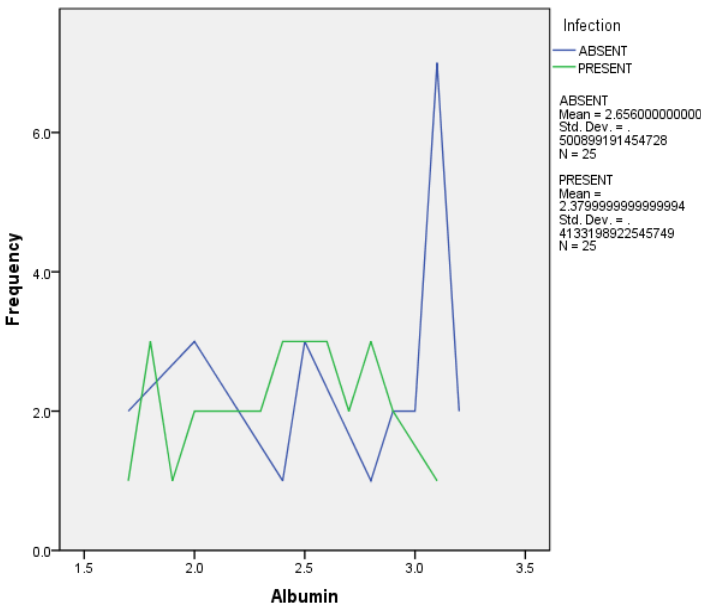


Fig. 22: Correlation with serum creatinine

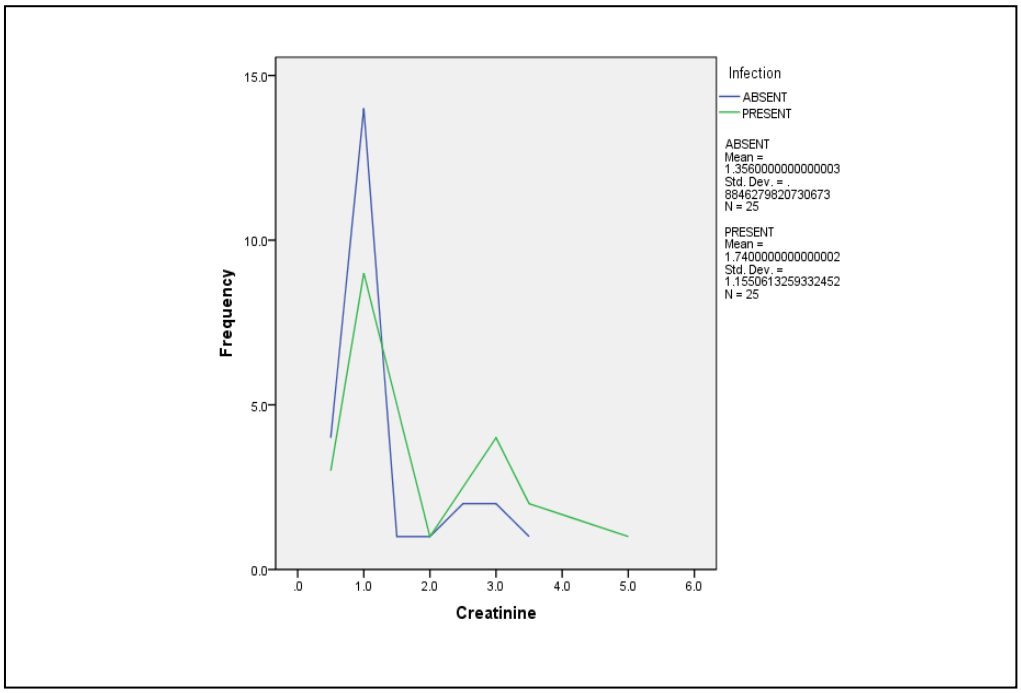
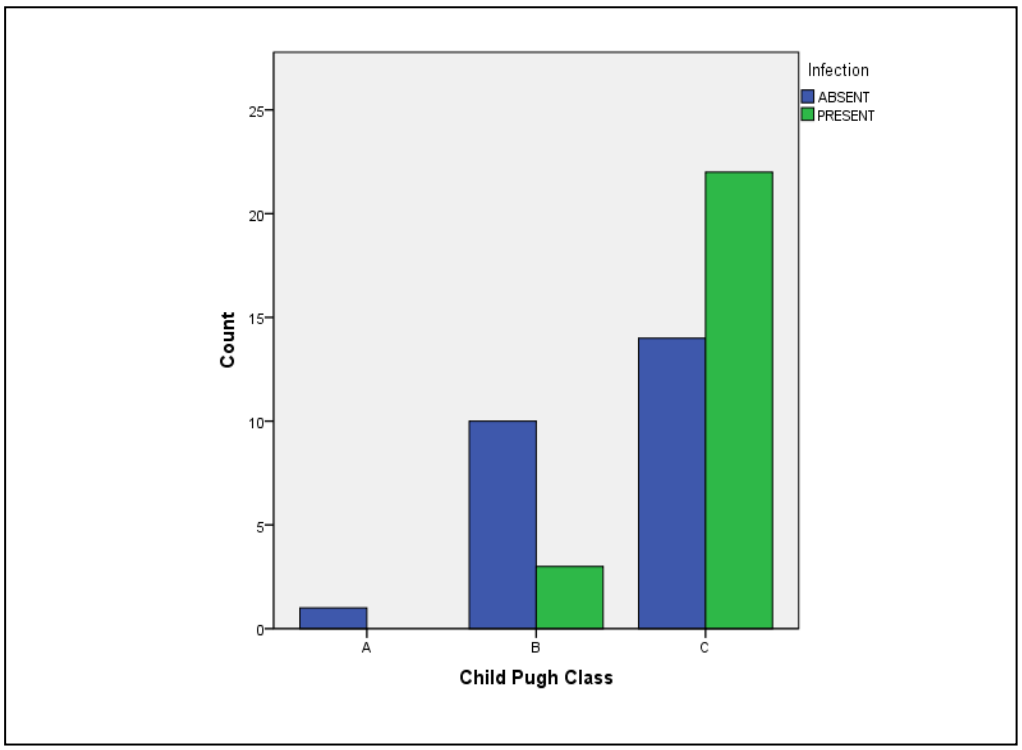


Fig. 23: Correlation with Child-Pugh class



OBSERVATIONS

The study was carried out in the Departments of Medicine and Microbiology at the Govt Kilpauk medical college & Hospital, Kilpauk, Chennai on 50 patients of liver cirrhosis satisfying the inclusion and exclusion criteria. The patients were assessed for the presence of various infections like spontaneous bacterial peritonitis (SBP) and its variants, spontaneous bacteremia, urinary tract infections (UTI), lower respiratory tract infections, cellulitis and spontaneous bacterial empyema and their prevalence was calculated. The study also aimed to find any association of bacterial infections in liver cirrhosis with various demographic and clinical factors like age, sex, gastrointestinal (GI) hemorrhage, Child Pugh class, H/o any invasive procedures, blood counts and various biochemical parameters.

DEMOGRAPHIC PROFILE OF THE STUDY GROUP:

Age and gender distribution:

The age of the subjects ranged from 22 to 70 years. The mean age was 48.8 ± 11.77 years. Age distribution of the patients is shown in Fig. 1. Most of the patients were between 41-50 years of age.

Of the 50 patients studied, 41 were male and 9 were female (Fig. 2).

History of gastrointestinal hemorrhage and invasive procedures:

Of the 50 subjects studied, 27 presented with a history of gastrointestinal hemorrhage within 1 week of presentation. Invasive procedures like upper GI endoscopy and bladder catheterization in the 2 weeks prior to the day of study had been done in 9 patients. The figures are shown in Table 4 and Fig. 3,4.

	H/O GI Hemorrhage		H/O Invasive Procedures	
	Frequency (n)	**Percentage (%)**	**Frequency (n)**	**Percentage (%)**
Absent	23	46.0	41	82.0
Present	27	54.0	9	18.0
Total	50	100.0	50	100.0

Table 4: History of GI hemorrhage and invasive procedures in the subjects

Etiology of cirrhosis:

The history of a daily alcohol intake of at least 60 g/day for at least 10 years for men and 20 g/day for women[203] was considered as significant alcohol consumption. History of significant alcoholism was present in 32 patients; all males (Table 4 and Fig. 5). HBsAg was reactive in 5 patients and Anti-HCV in 1 patient, making Hepatitis B and Hepatitis C respectively, the likely etiology of cirrhosis in these patients (Table 5 and Fig. 5).

Etiology of cirrhosis		
	Frequency (n)	**Percentage (%)**
Alcoholic liver disease	32	64
HBsAg reactive	5	10
Anti-HCV reactive	1	2
Cause unknown	12	24
Total	50	100

Table 5: Etiology of cirrhosis

Clinical and biochemical profile:

A detailed general physical and focused systemic examination was done in all patients. The vital signs measured in the studied population are shown in Table 6. .

Vital signs			
	Pulse Rate (per minute)	**Respiratory Rate (per minute)**	**Axillary Temperature (ºF)**
Mean	92.2	18.2	99.4
Std. Deviation	11.9	2.7	1.4

Table 6 : Vital signs

7 patients were found to be have systolic blood pressure (BP) <90 mmHg at the time of study, 42 patients had systolic BP in the range 90 to 140 mmHg and 1 had systolic BP >140 mmHg. The distribution of blood pressure among the patients is shown in Table 7 and Fig. 6.

BP		
Systolic blood pressure (mmHg)	**Frequency (n)**	**Percentage (%)**
<90	7	14.0
90-140	42	84.0
>140	1	2.0
Total	50	100.0

Table 7: Blood Pressure

Ascites was present in all the patients studied, varying from mild/moderate to massive (Table 8 and Fig. 7).

ASCITES		
	Frequency (n)	**Percentage**
Mild to moderate	24	48.0
Massive	26	52.0
Total	50	100.0

Table 8: Ascites

Encephalopathy was present in 24 cases, grade 1 or 2 in 16 patients and grade 3 or 4 in 8 (Table 9 and Fig. 8).

Encephalopathy		
	Frequency (n)	**Percentage**
Absent	26	52.0
Grade 1 or 2	16	32.0
Grade 3 or 4	8	16.0
Total	50	100.0

Table 9: Encephalopathy

The results of complete blood counts, liver function tests, kidney function tests are tabulated below. (Table 10, 11, 12, 13)

Complete blood count			
	Hb (g/dL)	**TLC (/mm^3)**	**Platelet (/mm^3)**
Mean	9.3	9164	86160
Std. Deviation	2.1	4843	44849

Table 10: Complete blood count

Liver function tests						
	Total bilirubin (mg/dL)	**AST (IU/L)**	**ALT (IU/L)**	**ALP (IU/L)**	**Total protein (g/dL)**	**Albumin (g/dL)**
Mean	3.7	92.0	73.3	296.0	5.9	2.5
Std. Deviation	4.1	94.9	84.1	246.6	.7	.5

Table 11: Liver function tests

Kidney function tests		
	Urea (mg/dL)	**Creatinine (mg/dL)**
Mean	59.4	1.5
Std. Deviation	48.0	1.0

Table 12: Kidney function tests

Coagulation profile		
	PT (sec)	**INR**
Mean	17.9	1.5
Std. Deviation	4.6	.4

Table 13: Prothrombin time (PT)/ International normalized ratio (INR)

Ascitic fluid was tapped in all cases and ascitic fluid protein and sugar were calculated and are tabulated below (Table 14).

Ascitic fluid characteristics		
	Ascitic Protein (g/dL)	**Ascitic Sugar (mg/dL)**
Mean	1.03	123.9
Std. Deviation	.39	31.1

Table 14: Ascitic fluid characteristics

Ascitic fluid total and differential white cell count was done and an absolute polymorphonuclear cell count ≥250 cells/cu.mm was considered significant for spontaneous bacterial peritonitis (Table 15)

Ascitic fluid PMN count	Frequency (n)	Percentage (%)
≥250 cells/cu. Mm	13	26.0
<250 cells/cu. Mm	37	74.0

Table 15: Ascitic fluid polymorphonuclear cell count

Child-Pugh score was calculated from the above parameters and tabulated. Child Pugh class A was seen in 1 patient (2%), B in 13 patients (26%) and C in 36 patients (72%). Findings are shown in Table 16 and Fig. 9.

Child Pugh Class		
	Frequency (n)	Percentage (%)
A	1	2.0
B	13	26.0
C	36	72.0
Total	50	100.0

Table 16: Child Pugh class

RESULTS OF THE STUDY

The subjects in the study were studied for various infections like spontaneous bacterial peritonitis (SBP) and its variants, spontaneous bacteremia, urinary tract infections (UTI), lower respiratory tract infections, cellulitis and spontaneous bacterial empyema.

Infections were detected in 25 out of the 50 patients (50%). 18 of the 50 patients (36%) had only one infection, while 7 of the 50 patients (14%) had two infections. The combination which was seen in the most number of cases was SBP and UTI (4 cases). SBP and its variants were present in 15 patients (30%), UTI in 8 patients (16%), spontaneous bacteremia in 4 patients (8%), lower respiratory tract infections in 3 patients (6%) and cellulitis and spontaneous bacterial empyema in 1 patient each (2%). Findings are shown in Table 17, 18 and Fig. 10.

Prevalence of Infection		
	Frequency (n)	**Percentage**
absent	25	50.0
present	25	50.0
Total	50	100.0

Table 17: Prevalence of infections

Of the 15 cases of SBP and its variants, 7 cases were culture negative neutrocytic ascites, 2 cases were monobacterial non-neutrocytic bacterascites and 6 cases satisfied both polymorphonuclear count and culture criteria for diagnosis of SBP. *Escherichia coli* was grown in 3 cases, *Klebsiella spp.* in 3, and *Citrobacter spp*.and *Enterococcus spp*. in one case each.

UTIs were present in 8 cases, all eight of whom had greater than 15 pus cells/hpf on routine microscopic examination. 3 cases were culture positive. *E.coli* was grown in 2 cases and *Klebsiella* in one.

In the cases of spontaneous bacteremia, *Staphylococcus aureus* was cultured in 3 cases and *Enterococcus spp*. in one. Out of the 3 cases of lower respiratory tract infections, one was culture positive with *E.coli*. The solitary case of cellulitis grew *Klebsiella spp*. and the case of spontaneous bacterial empyema was culture negative.

Prevalence of different infections		
	Frequency (n)	**Percentage**
SBP and its variants	15	30.0
UTI	8	16.0
Bacteremia	4	8.0
LRTI	3	6.0
Cellulitis	1	2.0
Others	1	2.0

Table 18: Prevalence of different infections

Of the total 17 cases which were culture positive, *E.coli* was grown in 6 cases, *Klebsiella* was grown in 5 cases, *Staphylococcus aureus* in 3 cases, *Enterococcus* spp. in 2 cases and *Citrobacter* spp. in one. Findings are shown in Table 19 and Fig. 11.

Organisms grown on culture	
	Frequency (n=17)
E.coli	6
Klebsiella spp.	5
Staph. aureus	3
Enterococcus spp.	2
Citrobacter spp.	1

Table 19: Organisms grown on culture

ASSOCIATION WITH VARIOUS FACTORS

The association of bacterial infections with various demographic parameters like age, gender, clinical parameters like gastrointestinal hemorrhage, history of invasive procedures, ascites, encephalopathy, Child-Pugh score, complete blood counts, liver function tests, kidney function tests and PT/INR was also studied.

AGE

The mean age of the patients with infections was 48.0 ± 11.372 years and in those without infections was 49.6 ± 12.336 years. There was no significant statistical difference between the two groups (p=0.636).

GENDER

20 out of 41 (48.8%) male patients recruited in this study presented with infections, while 5 out of 9 (55.6%) female patients had one of the infections. No significant difference was found between the two genders (p=0.713). Findings are shown in Fig. 12.

HISTORY OF GI HEMORRHAGE

17 out of 27 patients (63%) who had a history of GI hemorrhage within 1 week of the study had one of the infections, while 8 out of 23 (34.8%) patients without that history had infections. The study shows that patients with history of GI hemorrhage are more likely to have infections (p=0.047). Findings are shown in Table 20 and Fig. 13.

HISTORY OF INVASIVE PROCEDURES

5 out of 9 patients (55.6%) with history of invasive procedures within 2 weeks of the study had infections, while 20 out of 41(48.78%) without that history had infections. These data show that invasive procedures did not cause a significant predisposition to infections in our study. Findings are shown in Table 20 and Fig. 14.

Correlation with history of GI hemorrhage and invasive procedures.				
		Ratio	**Percentage (%)**	**p-value**
Infections	With GI hemorrhage	17/27	63.0	**0.047**
	Without GI hemorrhage	8/23	34.8	
Infections	With inv. procedure	5/9	55.6	0.713
	Without inv. procedure	20/21	48.8	

Table 20: Correlation with history of GI hemorrhage and invasive procedures

ETIOLOGY OF CIRRHOSIS

14 out of 32 (43.8%) patients who had alcoholic liver disease as the cause of cirrhosis presented with infections while 11 out of 18 (61.1%) without a history of significant alcohol intake. Alcoholic liver disease did not seem to increase the predisposition to infections (p=0.239). 3 out 5 patients who tested to be HBsAg reactive had infections and the one patient who was Anti-HCV reactive also had infection. The study did not have adequate number of HBsAg or Anti-HCV reactive patients to derive a correlation with infections.

CLINICAL PARAMETERS

BLOOD PRESSURE

5 out of 7 (71.4%) patients who had systolic BP <90 mmHg turned out to have infections. 19 of the 42 (45.2%) patients with systolic BP between 90 and 140 mmHg had infections and the one patient who was had systolic BP >140 mmHg had infection. There were not enough subjects in each group to arrive at a statistically significant correlation between blood pressure and infections. Findings are shown in Fig. 15.

PULSE RATE

The mean pulse rate in the patients with infections was 95.4 ± 13.1 per minute, and in those without infections was 88.9 ± 9.8 per minute. The pulse rate tended to correlate with infections with an almost significant p-value of 0.054. Findings are shown in Table 21 and Fig. 16.

RESPIRATORY RATE

The mean respiratory rate of those with infections was 19.2 ± 3.1 per minute, while those without infections had 17.2 ± 1.6. The respiratory rate seemed to significantly correlate with infections (p=0.006). Findings are shown in Table 21 and Fig. 17.

AXILLARY TEMPERATURE:

The mean axillary temperature of those with infections was 99.8 ± 1.6 ºF, while those without infections had 98.9 ± 0.8 ºF. The axillary temperature seemed to significantly correlate with infections (p=0.011). Findings are shown in Table 21 and Fig. 18.

Correlation with vital signs				
		Mean	**Standard deviation**	**p-value**
Pulse rate	With infection	95.4	13.1	**0.054**
	Without infection	88.9	9.8	
Respiratory rate	With infection	19.2	3.1	**0.006**
	Without infection	17.2	1.6	
Axillary temperature	With infection	99.8	1.6	**0.011**
	Without infection	98.9	0.8	

Table 21: Correlation with vital signs

ASCITES

All patients had some degree of ascites. 10 out of 24 (41.7%) patients with mild-moderate ascites had infections, while 15 out of 26 (57.7%) patients with severe ascites had infections (p-value=0.258). Patients with the higher grade of ascites had a greater chance of infection but the association was not statistically significant. Findings are shown in Table 22.

Patients with a higher grade of encephalopathy tended to have a higher chance of infection. 11 out of 26 (42.3%) with no encephalopathy, 7 out of 16 (43.8%) with grade 1 or 2 encephalopathy and 7 out of 8 (87.5%) with grade 3 or 4 encephalopathy had infections. The statistical correlation was almost significant with a p-value of 0.068. Chi square test for trends showed a p-value of 0.059. Findings are shown in Table 22.

Correlation with grade of ascites and encephalopathy			
	Grading	**Prevalence of infections (%)**	**p-value**
Ascites	Mild-moderate	41.7	0.258
	Severe	57.7	
Encephalopathy	Absent	42.3	0.068
	Mild-moderate	43.8	
	Severe	87.5	

Table 22: Correlation with severity of ascites and encephalopathy

LABORATORY PARAMETERS

COMPLETE BLOOD COUNT

Platelet count was found to be lower in patients with infections (mean 71640 ± 40751) than in those without infections (mean 100680 ± 44797). The correlation was statistically significant with a p-value of 0.020. Hemoglobin (p= 0.745) and total leucocyte count (p= 0.541) did not have any correlation with infections. In contrast to common perception, mean TLC count was higher in those without infections. Findings are shown in Table 23 and Fig. 19.

Complete blood count				
	Infection	**Mean**	**Std. Deviation**	**p-value**
Hemoglobin	Present	9.2	2.0	0.745
	Absent	9.4	2.1	
TLC	Present	8740	4695.9	0.541
	Absent	9588	5046.7	
Platelet	Present	71640	40751.2	**0.020**
	Absent	100680	44796.5	

Table 23: Correlation with Complete blood count

LIVER FUNCTION TESTS:

Serum total protein (p= 0.024) and serum albumin (p= 0.039) correlated significantly with the presence of infections. Alkaline phosphatase also seemed to correlate with infections with a p-value of 0.014. Findings are shown in Table 24 and Fig. 20,21.

Serum bilirubin (p= 0.869), aspartate transaminase (p= 0.169) and alanine transaminase (p= 0.219) did not correlate with the presence of infections.

Liver function tests				
	Infection	**Mean**	**Std. Deviation**	**p-value**
Total bilirubin	Present	3.8	3.8	0.869
	Absent	3.6	4.5	
AST	Present	74.6	87.8	0.196
	Absent	109.5	100.1	
ALT	Present	58.8	37.2	0.219
	Absent	88	112.2	
ALP	Present	380.2	317.6	**0.014**
	Absent	211.8	92.2	
Total protein	Present	5.7	0.7	**0.024**
	Absent	6.1	0.6	
Albumin	Present	2.4	0.4	**0.039**
	Absent	2.7	0.5	

Table 24: Correlation with Liver function tests

KIDNEY FUNCTION TESTS:

The mean value of urea in patients with infections was 65.1 ± 44.4 mg/dL and in those without infections was 53.7 ± 51.7 mg/dL and the correlation was not significant (p= 0.405). The mean value of creatinine in patients with infections was 1.7 ± 0.9 mg/dL and in those without infections was 1.6 ± 0.4 mg/dL and the correlation was not significant (p= 0.193). Findings are shown in Table 25 and Fig. 22.

Kidney function tests				
	Infection	**Mean**	**Std. Deviation**	**p-value**
Urea	Present	65.1	44.4	0.405
	Absent	53.7	51.7	
Creatinine	Present	1.7	0.9	0.193
	Absent	1.6	0.5	

Table 25: Correlation with Kidney function tests

INR:

The mean value of INR in patients with infections was 1.6 ± 0.5 and in those without infections was 1.5 ± 0.3 and the correlation was not significant (p= 0.348).

ASCITIC FLUID CHARACTERISTICS

ASCITIC FLUID PROTEIN

The mean value of ascitic fluid protein in patients with infections was 1.1 ± 0.4 mg/dL and in those without infections was 1.004 ± 0.3 mg/dL and the correlation was not significant (p= 0.588).

ASCITIC FLUID SUGAR

The mean value of ascitic fluid sugar in patients with infections was 120.6 ± 39.7 mg/dL and in those without infections was 127.2 ± 19.3 mg/dL and the correlation was not significant (p= 0.458).

CHILD-PUGH SCORE

Child-Pugh score correlated with infections (p= 0.038) with 22 out of 36 (61.1%) patients with Child-Pugh class C having infections, while only 3 out of 13

(23.1%) with Child-Pugh class B had infections. Chi square test for trends showed a p-value of 0.028. Findings are shown in Table 26 and Fig. 23.

CHILD PUGH SCORE					
	Infection	**A**	**B**	**C**	**p-value**
Infections	Present	0	3	22	**0.038**
	Absent	1	10	14	
	Percentage	0	23.1	61.1	

Table 26: Correlation with Child-Pugh score

DISCUSSION

The study was undertaken in the departments of Medicine and Microbiology at Govt Kilpauk Medical College & Hospital, Kilpauk, Chennai. The aim of the study was to study bacterial infections in liver cirrhosis and estimate their prevalence in patients with cirrhosis. Patients of cirrhosis were assessed for the presence of infections like spontaneous bacteremia, spontaneous bacterial peritonitis and its variants, urinary tract infections, lower respiratory tract infections, skin infections, spontaneous bacterial empyema and meningitis.

We also looked for the association of bacterial infections in liver cirrhosis with demographic and clinical factors like age, sex, gastrointestinal (GI) hemorrhage, Child Pugh class, H/o any invasive procedures and various laboratory parameters.

A total of 50 patients were studied. There were 41 male and 9 female patients in the study. The age of the subjects ranged from 22 to 70 years. Most of the patients were between the ages 41-50. Patients, who had not received antibiotics in the past one week, were evaluated for the presence of infections before the institution of antibiotics.

In the present study, infections were detected in 25 out of 50 patients with cirrhosis (50%). 32 infections were detected in total. 18 of the 25 patients (72%) with infections had one infection and the remaining 7 had two infections (28%). Of the 7 patients who had two infections, four had a combination of SBP and UTI, two had SBP and pneumonia and one had SBP and SBE. Several studies have been done to estimate the prevalence of bacterial infections in cirrhosis. On an average, bacterial infections have been diagnosed in a third of the (range of 25% to 47%) patients who are admitted with a diagnosis of cirrhosis.[9-12]

A prospective study by Caly WR et al in 1993 found out that bacterial infections were present in 47.06% (80 out of 170) of patients with cirrhosis.[9] A multicenter prospective study by Borzio M et al estimated bacterial infections in 34% patients in cirrhosis (150 out of 405 patients, 89 community acquired, 61 health-care associated).[10] In a study by Fernández J et al reported in 2002, a total of 1567 admissions of cirrhotic patients were studied. 572 bacterial infections were diagnosed in 507 admissions (32%).[11] The US nationwide sample identified 65,072 patients in 2006 with a discharge diagnosis of cirrhosis. Of the hospitalized patients, 26,300 (40.41% of the total) had presumed infection.[18]

Thus the results of the present study are similar to those reported in the literature.

Of the infections diagnosed, SBP and its variants were the most common with 15 cases (46.8%). UTIs formed 8 cases (25%), spontaneous bacteremia 4 (12.5%), pneumonia 3 (9.3%) and spontaneous bacterial empyema one case (3.1%) of the total infections. In the study by Caly WR et al, of the infections diagnosed, 31.07% were SBP and its variants, 25.24% were UTI, and pneumonia in 21.37% cases.[9] In the study by Borzio M et al, 41% of the infections were UTIs, 23% were SBP, 23% were bacteremia and 17% were lower respiratory infections.[10] In the study by Fernandez J et al, out of the 572 infections, 138 were SBP (24.12%), 111 were UTI (19.4%), 78 were pneumonia (13.63%) and 45 were bacteremia (7.86%).[11]

It has been well established that infections can be missed in patients of cirrhosis because most of them are culture negative. 34% of the patients (17 out of 50) or 53.125% of the infections detected (17 out of 32) in our study were culture positive. This correlates with the figures quoted by various reviews. A review by

Pleguezuelo M et al stated that 40-70% of the infections in cirrhosis were culture positive.[17] The NACSELD report under Bajaj JS et al stated that 30-50% of infections in cirrhosis were culture negative.[18] An Indian review by Taneja SK and Dhiman RK reported that the prevalence of culture positivity was 50-70%.[133]

8 out of the 15 patients (53.33%) detected to be SBP were culture positive. According to the EASL clinical practice guidelines published in 2010, 40% of SBP were culture positive.[91]

The present study found that 12 out of 17 (70.58%) patients who were culture positive, were infected with Gram negative bacteria. *Escherichia coli* was grown in cultures of 6 patients, *Klebsiella spp.* in 5 cases, *Staphylococcus aureus* in 3 cases, *Enterococcus* species in 2 cases and *Citrobacter* species in one. The study by Caly WR found Gram negative infections in 72.34% of the cases.[9] The review by Pleguezuelo M et al stated that the Gram negative infections formed 60% of all infections.[17] In a study by Kuo CH et al, Gram negative bacteria were the predominant microorganisms of bacteremia (75.6%). Among them, *Escherichia coli, Klebsiella pneumoniae and Aeromonas hydrophilia* were the three most commonly detected microorganisms.[5]

The findings of our study are thus in accordance with the fact that most of the infections in cirrhosis are caused by Gram negative enteric bacteria which translocate via intestinal mucosa. But because of irrational use of antibiotics, the recent trend of infections shows a predominance of Gram positive organisms of almost 60%. Most of these infections are nosocomial. Several studies by Fernández J et al[11], Reuken PA et al[52] and Campillo B et al[84] reinforce these recent changes in microbial patterns in cirrhosis.

82.35% of the culture positive cases in our study were composed of enteric flora. The study by Borzio M et al stated that 62% of the infections in cirrhosis were caused by gut bacteria.[10] A study by Bruns T and Stallmach A reported that bacterial translocation from intestinal bacteria and bacterial products into mesenteric lymph nodes and subsequent systemic circulation was responsible for 95% of the cases of SBP.[16]

Age and gender did not seem to correlate in our study with the presence of infection. A study by Reuken PA et al found an association between increasing age, female gender and UTIs in patients with cirrhosis.[103] No other study found any association between age and gender and the development of infections in cirrhosis.

In this study, patients who had a history suggestive of GI hemorrhage within 1 week of the study had a greater chance of infections than those without that history (63% vs 34.8%, p-value <0.05). There are several studies which have studied this association. A study by Gerbes AL et al stated that GI bleeding facilitated infections and in addition, infections caused an increased rate of bleeding.[90] A meta-analysis by Chavez-Tapia NC et al found out that following GI bleeding, 15% of patients who did not receive antibiotic prophylaxis developed bacteremia, while only 3% who got antibiotic prophylaxis developed bacteremia.[92,93] This shows a 75% reduction in the risk of bacteremia with antibiotic prophylaxis. GI bleeding also increased the rates of re-bleeding, average hospital stay and mortality. The increased prevalence was seen with all infections like SBP, UTI and pneumonia. Thus the European association for the study of the liver (EASL) recommends antibiotic prophylaxis following GI bleeding in all cases[91].

In our study, invasive procedures up to 2 weeks prior to the study did not seem to cause an increase in the incidence of infections (55.6% vs 48.8%, p= 0.713). While some studies like the one by Banerjee S et al found an increase in the incidence of infections following upper GI endoscopy,[86] studies like the one by Llach J et al did not find an association between colonoscopy and infections.[87] Currently there are no recommendations for antibiotic prophylaxis prior to or following invasive procedures.

In our study, patients with a significant history of alcohol intake tended to have a greater risk of infection compared to no-alcoholics (61.1% vs 43.8%) but the association was not statistically significant (p= 0.239). A retrospective study by Rosa H et al found that alcoholic cirrhotics of Child Pugh class A or B had a greater chance of infection compared to non-cirrhotic alcoholics, while no difference was seen between alcoholics and non-alcoholics of Child Pugh class C.[101] This shows that there are other factors at play causing infections, like the severity of liver disease but modifiable risk factors like alcohol intake should always be corrected.

In the present study, patients with infections had higher values of certain parameters associated with systemic inflammatory response syndrome (SIRS) than those without infections and all these correlations were statistically significant. Pulse rate (p= 0.05), respiratory rate (p= 0.006) and axillary temperature (p= 0.011) were all higher in patients with infections. Various studies have tried to study this association. A study by Reuken PA et al[103] and a review by Bruns T et al[104] both underline the fact that SIRS is more common in cirrhosis with infections (67% vs 37%). But because of the hyperdynamic circulation and tense ascites in cirrhosis, SIRS criteria are less specific in cirrhosis compared to the general population.[104]

Our study found that patients with severe ascites had a greater chance of infection compared to those with mild to moderate ascites but the correlation was not statistically significant (57.7% vs 41.7%, p= 0.258). In the landmark study by Arvaniti V et al in 2010 which showed that infections increased the mortality in cirrhosis four-fold, it was found that bacterial infections were related to the severity of liver disease as defined by composite scores like MELD score or Child Pugh score, but the degree of ascites was never found to be the sole determinant of infections.[13]

A study by Merli M et al in 2013 found that infections are an independent predictor of cognitive impairment or hepatic encephalopathy in cirrhosis and alterations in sensorium were strongly related to the infectious episode and reversible after its resolution.[120] In our study, patients with a higher grade of encephalopathy tended to have a higher chance of infections. 11 out of 26 (42.3%) with no encephalopathy, 7 out of 16 (43.8%) with mild to moderate encephalopathy and 7 out of 8 (87.5%) with severe encephalopathy had infections (p= 0.068). According to the study by Jalan R et al, patients with cirrhosis and an acute organ failure like encephalopathy are at a greater risk of short-term mortality.[77]

Patients with infections had a lower platelet count with a mean of 71640 ± 40751.2 per cu.mm compared to those without infections with a mean platelet count of 100680 ± 44796.5. This correlation was statistically significant with a p-value of 0.020. A study by Guarner C et al found that platelet count <98,000 per cu.mm independently correlated with the risk of developing the first spontaneous [bacterial peritonitis episode.[94] This finding reinforces the recent recommendations by EASL of giving antibiotic prophylaxis at a platelet count less than 98,000 cells per cu.mm.[57] The study did not find a correlation between hemoglobin (p= 0.745) or total

leucocyte count (p= 0.541) and infections. This is contrary to popular belief and probably explains why total leucocyte count is not part of the CLIF-SOFA score proposed by the CANONIC study, which predicts prognosis and mortality in patients of cirrhosis with infections.[5]

Among the 18 variables that were significantly associated with death after bacterial infections in three or more studies evaluated by Arvaniti V et al, five were related to liver function or severity of cirrhosis (Child-Pugh score, prothrombin time/INR, bilirubin, albumin, and MELD score).[13] In the present study, serum total protein (p= 0.024) and serum albumin (p= 0.039) correlated significantly with the presence of infections. Alkaline phosphatase also seemed to correlate with infections with a p-value of 0.014. Serum bilirubin (p= 0.869), aspartate transaminase (p= 0.169) and alanine transaminase (p= 0.219) did not correlate with the presence of infections. Serum albumin is part of liver disease severity scores like Child Pugh and MELD and its inverse relation with infections could be due to infections being common in those with the more severe liver disease.[104] Alkanine phosphatase seems to have an association with infections in our study but this association needs elucidation. Increased serum bilirubin which has been widely reported (Guarner C et al) as being associated with infections did not correlate with infections in our study.[94]

Both blood urea (p= 0.405) and serum creatinine (p= 0.193) tended to be higher in patients with infections. But neither of the relations was statistically significant. In a study by Belcher JM et al, it was found that the incidence of mortality, general medical events (bacteremia, pneumonia, urinary tract infection), and cirrhosis-specific complications increases with the severity of AKI.[119] EASL

recommends antibiotic prophylaxis at a serum creatinine >1.2 mg/dl or BUN >25 mg/dl.[57]

Ascitic fluid protein has been strongly associated in cirrhosis with infections as shown by studies like Guarner C et al.[94] Primary prophylaxis for SBP is recommended at an ascitic fluid protein <1.5 g/dL.[11,12,191,192] Low ascitic fluid protein is seen to be associated with greater incidence of pathological bacterial translocation. In our study, 46 out of the 50 patients had an ascitic fluid protein <1.5 g/dL. Ascitic fluid protein did not correlate with infections and this was probably because of the low sample size.

Child-Pugh score correlated positively with infections (p= 0.038) with 22 out of 36 (61.1%) patients with Child-Pugh class C having infections, while 3 out of 13 (23.1%) patients of Child-Pugh class B had infections. Various studies have shown that a higher Child Pugh class is associated with a greater risk of infection (Caly WR et al[9] (1993), Borzio M et al[10] (2001), Gines P et al[191] (2010), Moreau R et al[5] (2013). EASL guidelines (2013) recommend antibiotic prophylaxis at a Child Pugh score ≥9.[57]

SUMMARY

The study was carried out in patients of liver cirrhosis. Patients were assessed for the presence of infections like spontaneous bacteremia, spontaneous bacterial peritonitis and its variants, urinary tract infections, lower respiratory tract infections, skin infections, spontaneous bacterial empyema and meningitis. The association of bacterial infections in liver cirrhosis with demographic and clinical factors like age, sex, gastrointestinal (GI) hemorrhage, Child Pugh class, H/o any invasive procedures and various laboratory parameters was evaluated.

- A total of 50 patients of liver cirrhosis were studied.
- There were 41 male and 9 female patients in the study.
- The age of the subjects ranged from 22 to 70 years. The mean age was 48.8 ± 11.77 years. Most of the patients were between the ages 41-50.
- 27 out of the 50 (54%) patients presented with a history of gastrointestinal hemorrhage, upper or lower, within 1 week of presentation.
- Invasive procedures like upper GI endoscopy and bladder catheterization in the 2 weeks prior to the day of study had been done in 9 (18%) of the patients.
- 32 (64%) patients had a history of significant alcoholism (at least 60 g/day for at least 10 years for men and 20g/day for women).
- HBsAg was reactive in 5 patients and Anti-HCV was reactive in 1 patient.
- 7 (14%) patients were found to be in hypotension (systolic BP<90 mmHg) at the time of study, 42 (84%) in the normotensive range (systolic BP between

90-140 mmHg) and 1 (2%) in the hypertensive range (systolic BP>140 mmHg).

- The mean pulse rate of the patients was 92.2 ± 11.9 per minute, the mean respiratory rate was 18.2 ± 2.7 per minute and the mean axillary temperature of the patients was 99.4 ± 1.4 ºF.
- Mild to moderate ascites was present in 24 (48%) patients and massive ascites in 26 (52%) patients.
- Encephalopathy was present in 24 (48%) cases, grade 1 or 2 in 16 (32%) patients and grade 3 or 4 in 8 (16%).
- 13 (26%) patients belonged to Child Pugh to class B, 36 (72%) to class C and 1 (2%) to class A.
- Bacterial infections were present in 25 out of the 50 patients (50%). 18 of the 25 patients (72%) with infections had one infection and the remaining 7 had two infections (28%). Of the 7 patients who had two infections, four had a combination of SBP and UTI, two had SBP and pneumonia and one had SBP and SBE
- 32 infections were detected in total. Of these, SBP and its variants were the most common (46.8%). UTIs formed 25%, spontaneous bacteremia 12.5%, pneumonia 9.3% and spontaneous bacterial empyema 3.1% of the total infections.
- 17 out of the 50 (34%) patients or 17 out of the 32 infections detected (53.125%) in our study were culture positive.

- 8 out of the 15 patients (53.33%) detected to be SBP were culture positive. 3 out the 8 patients (37.5%) of UTIs were culture positive.

- 12 out of the 17 patients (70.58%) who were culture positive were infected with Gram negative bacteria.

- *Escherichia coli* was grown in cultures of 6 patients, *Klebsiella* spp. was grown in 5 cases, *Staphylococcus aureus* in 3 cases, *Enterococcus* species in 2 cases and *Citrobacter* species in one.

- Age and gender did not seem to correlate in our study with the presence of infection.

- Patients who had a history of GI hemorrhage within 1 week of the study had a greater chance of infections than those without that history (63% vs 34.8%, p-value= 0.047).

- Invasive procedures up to 2 weeks prior to the study did not seem to cause an increase in the incidence of infections (55.6% vs 48.8%, p= 0.713).

- Patients with a significant history of alcohol intake tended to have a greater risk of infection compared to non-alcoholics (61.1% vs 43.8%) but the association was not statistically significant (p= 0.239).

- Patients with infection had a significantly higher pulse rate (95.4 ± 13.1 vs 88.9 ± 9.8) than those without infection (p-value= 0.05). Patients with infection had a significantly higher respiratory rate (19.2 ± 3.1 vs 17.2 ± 1.6) than those without infection (p-value= 0.006). Patients with infection had a

significantly higher axillary temperature (99.8 ± 1.6 vs 98.9 ± 0.8) than those without infection (p-value= 0.011).

- Patients with severe ascites had a greater chance of infection compared to those with mild to moderate ascites but the correlation was not statistically significant (57.7% vs 41.7%, p= 0.258).

- Patients with a higher grade of encephalopathy tended to have a higher chance of infections (42.3%- no encephalopathy, 43.8%- mild to moderate encephalopathy and 87.5%- severe encephalopathy, p= 0.068).

- Patients with infections had a significantly lower platelet count with a mean of 71640 ± 40751.2 per cu.mm compared to those without infections with a mean platelet count of 100680 ± 44796.5; p-value= 0.020. The study did not find a correlation between hemoglobin (p= 0.745), total leucocyte count (p= 0.541) and infections.

- Among the parameters in the liver function tests, serum total protein (5.7 ± 0.7 vs 6.1 ± 0.6; p= 0.024), serum albumin (2.4 ± 0.4 vs 2.7 ± 0.5; p= 0.039) and alkaline phosphatase (380.2 ± 317.6 vs 211.8 ± 92.2; p= 0.014) correlated significantly with the presence of infections. Serum bilirubin (p= 0.869), aspartate transaminase (p= 0.169) and alanine transaminase (p= 0.219) did not correlate with the presence of infections.

- Blood urea (65.1 ± 44.4 vs 55.7 ± 51.7; p= 0.405) and serum creatinine (1.7 ± 0.9 vs 1.6 ± 0.4; p= 0.193) tended to be higher in patients with infections.

- International normalized ratio (INR) (1.6 ± 0.5 vs 1.5 ± 0.3; p= 0.348) did not correlate with infections.

- There was no significant difference in ascitic fluid protein in patients with infections (1.1 ± 0.5 mg/dL) and in those without infections (1.0 ± 0.3 mg/dL); p= 0.588.

- Child-Pugh score correlated positively with infections (p= 0.038) with 61.1% of patients with Child-Pugh class C having infections, while 23.1% of Child-Pugh class B had infections.

CONCLUSION

Liver cirrhosis is one of the most common causes of mortality worldwide, ranking 18th on WHO's list of leading causes of death among all ages.[204] A vast majority of causes of cirrhosis are related to life style factors like alcoholism and preventable infectious diseases like Hepatitis B and Hepatitis C. Once cirrhosis ensues, it brings with it a whole gamut of complications which lead to disability and death. The most common cause of acute decompensation and acute-on-chronic liver failure in these patients is bacterial infection.

Bacterial infections in cirrhosis do not present as in normal individuals with fever and other features of SIRS and are mostly asymptomatic. Hence all patients of cirrhosis with acute decompensation or acute-on-chronic liver failure should be seen as possibly infected and be investigated for bacterial infections.

In this study, we found out that the prevalence of bacterial infections in cirrhosis was 50%. A total of 32 infections were detected. 18 of the 50 patients (36%) had only one infection, while 7 (14%) had two infections. Of all infections detected, SBP and its variants were the most common (46.8%). UTIs comprised 25%, spontaneous bacteremia 12.5%, pneumonia 9.3%, cellulitis and spontaneous bacterial empyema 3.1% each of the total infections. These figures are similar to the prevalence figures reported in various studies worldwide.

In our study, the clinical factors that were significantly associated with bacterial infections were GI hemorrhage, advanced liver failure (Child-Pugh class C), lower platelet count and lower serum protein and albumin.

Thus bacterial infections were commonly detected in patients of cirrhosis, with certain clinical factors being associated with this complication. Prophylactic antibiotics are hence indicated in these high risk groups. Also needed are novel markers of infection, which would help in the early diagnosis of infections in patients of cirrhosis, so that prompt institution of antibiotic therapy can be done, given the high morbidity and mortality associated with this complication.

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ANNEXURES

CASE PROFORMA	
Name	
Gender	Male [___]☐ Female ☐[___]
Hospital No.	[__I__I__I__I__I__]
Age	[___] years
Date of admission	[___]-[___]-[_____]
Date of discharge	[___]-[___]-[_____]
HISTORY	
Presenting complaints	
H/o presenting complaints	
H/o CAD, CVA, CKD	
H/o GI Hemorrhage	
H/o invasive procedures	
Personal history	
Family history	

GENERAL EXAMINATION	
Pulse (per minute): [____]	Respiratory Rate(per minute): [____]
Heart Rate (per minute): [____]	Axillary Temperature: [____].[__] °C
Blood Pressure	[____ /____] mmHg
Pallor	[yes] [no]
Icterus	[yes] [no]
Clubbing	[yes] [no]
Cyanosis	[yes] [no]
Pedal Edema	[yes] [no]
Lymphadenopathy	[yes] [no]
SYSTEMIC EXAMINATION	
Cardiovascular system	
Respiratory system	
Per-abdominal examination:	
Central Nervous system:	
Diagnosis:	

INVESTIGATIONS	
Complete blood count:	
Liver function tests:	
Kidney function tests with serum electrolytes:	
Prothrombin time/INR:	
CHILD-PUGH SCORE	
Serum Bilirubin	[1] [2] [3]
Serum Albumin	[1] [2] [3]
Prothrombin Time/INR	[1] [2] [3]
Ascites	[1] [2] [3]
Encephalopathy	[1] [2] [3]
TOTAL	
Class	[A] [B] [C]
Urine routine and microscopy:	
USG Abdomen:	
Ascitic fluid characteristics:	
Ascitic,blood,urine,sputum,skin lesion Cultures done and results:	

சுயஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு கல்லீரல் கரணை நோயில் ஏற்படும் தொற்றா நோய் பற்றிய ஆய்வு.

இடம்: பொது மருத்துவத்துறை

அரசு கீழ்பாக்கம் மருத்துவ கல்லூரி மருத்துவமனை

சென்னை

பங்குபெறுபவரின் பெயர்:

பங்குபெறுபவரின் வயது: **பங்குபெறுபவரின் எண்:**

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. நான் இவ்வாய்வில் தன்னிச்சையாக பங்கேற்கிறேன். எந்த காரணத்தினாலோ நான் சட்டசிக்கல்களும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக்கொள்ளலாம் என்றும் அறிந்துகொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்தோ மேலும் ஆய்வு மேற்கொள்ளும்போதும் இந்த ஆய்வில் பங்கு பெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்துகொள்கிறேன். இந்த ஆய்வின் முடிவுகளை தொழில்நுட்பத்தை தொடர்புகொள்ள மறுக்க மாட்டேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் ஆய்வாளரின் கையொப்பம்

இடம் :

தேதி :

PATIENT CONSENT FORM

Study detail: **"A STUDY OF PREVALENCE OF BACTERIAL INFECTIONS IN PATIENTS WITH LIVER CIRRHOSIS."**

Study centre : GOVT. KILPAUK MEDICAL COLLEGE, CHENNAI-10
Patients Name :
Patients Age :
Identification Number :

Patient may check (✓) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well-being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

Signature/thumb impression:

Patients Name and Address: Place Date

Signature of investigator :

Study investigator's Name : Place Date

KEY TO MASTER CHART

GENDER
F = Female, M = Male,

H/O GI HEMORRHAGE, H/O INVASIVE PROCEDURES, H/O SIGNIFICANT ALCOHOLISM
0 = absent, 1 = present

PULSE RATE, RESP. RATE
Values per minute

AXILLARY TEMP.
Values in Fahrenheit

SYSTOLIC BLOOD PRESSURE
0- <90, 1- 90-140, 2- >140 (In mmHg)

PALLOR, ICTERUS, CYANOSIS, CLUBBING, PEDAL EDEMA , LYMPHADENOPATHY
0 = absent, 1= present

ASCITES
0 = NO, 1= mild-moderate, 2= massive

ENCEPHALOPATHY
0 = No, 1= Grade 1 or 2, 2= Grade 3 or 4

Hb, Tot_protein, Albumin, Globulin, Ascitic protein
Values in g/dL

TLC, Platelet, Ascitic Fluid TLC
Values in cells/mm^3

DLC, PCV, Ascitic polymorphs, Ascitic monomorphs
Expressed as %.

CVBilirubin_Tot, Bilirubin_I, Bilirubin_D, Urea, Creatinine, Ascitic sugar
Values in mg/dL

AST, ALT, ALP
Values in U/L

Sodium, Potassium
Values in mEq/L

PT
Value in seconds

HBsAg, Anti-HCV
0= non-reactive, 1= reactive

Urine R/M
0= <15 pus cells/hpf, 1= ≥15 pus cells/hpf

BLOOD CULTURE, ASCITIC FLUID CULTURE, URINE CULTURE, OTHER FLUIDS GROWTH
0= no growth, 1= growth present

PUS CULTURE, SPUTUM CULTURE
0= not done, 1= done but no growth, 2= done with growth

Positive growth, Ascitic_Positive growth, Urine_Positive growth, Pus_Positive growth, Spututm_Positive growth

1- *Klebsiella sp*., 2- *Escherichia coli*, 3- *Staphylococcus Aureus*, 4- *Citrobacter spp*., 5- *Enterococcus spp.*

OTHER FLUID CULTURES DONE
0= not done, 1= Pleural fluid, 2= CSF

Bacteremia, SBP and its variants, UTI, Cellulitis, Pneumonia, Infection
0= absent, 1= present

Others 0- absent, 1- spontaneous bacterial empyema, 2- meningitis

S No	Name	Gender	Age	H/O GI Haemorrhage	H/O Invasive Procedures	H/o Significant Alcoholism	Pulse Rate	Resp. Rate	Axillary Temp	BP	Pallor	Icterus	Clubbing	Cyanosis	Pedal Edema	Lymphadenopathy	Ascites	Encephalopathy	Hb	TLC
1	Anandhan	M	45	0	0	1	94	22	99	1	0	1	1	0	1	0	2	1	9.6	13,900
2	Babu	M	40	1	1	1	96	18	100.4	1	0	0	1	0	1	0	1	3	12.4	4300
3	Balakishnan	M	60	0	1	0	92	22	100.6	1	1	0	0	0	1	0	1	3	6.7	3700
4	Ramesh	M	43	1	0	0	92	26	99.6	1	1	1	1	0	1	0	2	3	11.4	4200
5	Madhivanan	M	45	0	0	1	76	18	100	1	1	1	0	0	1	0	2	1	5.9	5500
6	Amaran	M	50	1	0	1	78	18	100.4	1	1	1	0	0	1	0	1	1	10.4	6400
7	Gandhi	M	48	0	0	1	96	25	104.1	1	0	0	1	0	1	0	1	2	9.7	18900
8	Mani	M	35	0	0	1	106	26	102.8	0	1	1	0	0	0	0	1	3	7.2	12400
9	Sekar	M	70	0	0	1	88	20	99.8	1	0	1	0	0	1	0	1	2	9.7	9000
10	Indhira kumar	M	52	0	0	0	70	18	100	1	1	0	0	0	1	0	2	1	7.2	9000
11	Rajendran	M	54	1	0	1	82	20	99.8	1	0	1	1	0	1	0	1	2	9	12000
12	Thangapandi	M	35	1	0	1	112	18	100	1	1	1	0	0	1	0	2	2	7.6	4200
13	Lakshmi	F	27	0	0	0	90	16	98	1	1	1	0	0	1	0	1	1	4.9	1500
14	Pandiyan	M	40	1	0	1	90	16	99	1	1	1	0	0	1	0	2	1	10.7	11200
15	Subash	M	60	1	0	1	104	20	98.4	1	1	0	0	0	1	0	2	1	10.2	14000
16	Venkatesan	M	50	1	0	1	68	20	99	1	0	1	0	0	0	0	1	1	9.6	6900
17	Murali	M	40	1	0	1	110	20	99	0	1	1	0	0	0	0	1	1	5.6	4000
18	Murugan	M	48	1	0	0	100	16	97	1	1	1	0	0	1	0	2	1	6.2	2000
19	Rangasamy	M	62	1	0	1	77	18	98.5	2	1	0	0	0	1	0	2	1	8.7	6400
20	Jothi	F	22	1	0	0	125	16	100	1	1	1	0	0	1	0	1	2	5.7	7000
21	Mohamad riyaz	M	31	0	1	1	68	18	100	1	0	1	0	0	0	0	2	2	6.4	9900
22	Ramasamy	M	42	1	0	1	92	18	101.4	1	0	1	0	0	1	0	2	1	12.6	9000
23	Sarashwathi	F	50	0	0	0	80	14	99	1	1	1	0	0	0	0	1	1	8.5	8200
24	Venkatraman	M	60	1	0	1	85	16	98	1	1	1	0	0	1	0	2	1	7.2	6600
25	Manoharan	M	28	0	0	1	86	20	99	1	1	1	0	0	0	0	2	2	8	6500
26	Mohan	M	70	0	0	0	83	20	97	0	0	0	0	0	1	0	1	1	10.8	2700
27	Manimaran	M	52	0	0	1	84	16	98.5	1	0	1	0	0	0	0	2	1	12.8	20400
28	Gopi	M	57	1	1	1	86	16	98.4	1	1	0	0	0	1	0	2	2	10.5	4200
29	Ramayi	F	60	1	0	0	104	18	99	1	1	0	0	0	0	0	2	1	9.7	14000
30	Johnson	M	42	1	0	0	110	18	101	0	0	0	0	0	0	0	2	2	12.9	11800

S No	Neutrophil (DLC)	Lymphocytes(DLC)	(Eosinophil)DLC	DLC (Monocyte)	PCV	Platelet	Bilirubin_Total	Bilirubin_Direct	Bilirubin_Indirect	AST	ALT	ALP	Total protein	Albumin	Globulin	Urea	Creatinine	Sodium	Potassium	PT	INR	Child Pugh Score
1	82	18	0	0	27.1	69000	3.1	1.1	2	45	60	257	5.8	2.4	3.4	45	1.2	134	4.6	16.3	1.41	C
2	58	40	1	1	36.1	42000	3.7	2.3	1.4	60	71	211	6	2.6	3.4	22	0.5	129	5.1	28.4	2.5	C
3	45	39	4	12	22	150000	2	0.7	1.3	70	26	93	7.3	2.8	4.5	18	0.9	141	4.8	14.7	1.31	C
4	64	28	8	0	34.4	60000	6.25	2.41	3.84	88	71	561	5.6	2.3	3.3	21	0.7	127	4.6	12.7	1	C
5	66	32	2	0	16.2	174000	3.5	1.4	2.1	40	38	215	7	3.2	3.8	24	1	131	4.4	20.3	1.83	C
6	58	40	1	1	32.8	52000	3.7	1.4	2.3	60	51	71	5.9	2.2	3.7	22	0.5	120	2.7	15.4	1.43	C
7	90	10	0	0	28	80000	2.2	0.9	1.3	50	42	201	6	2.9	3.1	80	2.9	134	4.9	15.3	1.4	C
8	86	14	0	0	21.4	197000	1.25	0.58	0.67	47	28	325	5.5	2.1	3.4	213	5.1	143	6.5	19.1	1.74	C
9	72	24	2	2	28	110000	1.9	0.6	1.3	41	50	308	6.8	3.1	3.7	37	0.9	136	4.7	15.4	1.4	B
10	66	30	3	1	22.1	92000	1.2	0.3	0.9	40	42	308	6.1	2.9	3.2	51	1.2	134	5.1	17.6	1.5	B
11	88	10	2	0	27.2	80000	18.7	10.7	8	98	62	349	5.1	2	3.1	96	3	126	4.6	28	1.62	C
12	70	26	2	2	23	47000	8	3.9	4.1	71	80	311	4	1.7	2.3	10	0.5	131	143	20.8	1.1	C
13	80	20	0	0	14.5	102000	1.9	0.7	1.2	40	31	308	6	2.5	3.5	17	0.8	140	3.7	12	1.1	B
14	68	30	1	1	30.5	176000	2.2	1.3	0.9	125	93	235	5.2	1.7	3.5	93	2.7	138	4	17.6	1.11	C
15	80	18	2	0	31.4	90000	2	0.8	1.2	44	50	203	5.6	2.3	3.3	44	0.9	130	5.1	20.2	1.8	C
16	88	10	2	0	29.2	113000	12.6	9.4	3.2	105	39	486	5.4	2	3.4	98	3.3	143	4.4	12.7	1.02	C
17	70	26	2	2	14.9	62000	0.9	0.4	0.5	39	17	94	6.7	2.2	4.5	59	3.1	132	4.3	13.6	1.32	B
18	59	40	1	0	21.8	22000	2.5	1	1.5	24	31	243	4.9	1.8	3.1	34	0.9	128	3.2	22.1	1.45	C
19	65	32	1	1	24.1	114000	2	0.8	1.2	57	74	1687	5.6	2.1	3.5	66	2.9	141	4.3	13	0.97	B
20	70	24	5	1	19.3	40000	4.6	0.8	3.8	16	36	214	6	2.4	3.6	26	1.4	137	3.4	20.1	1.85	C
21	81	19	0	0	17.4	163000	6.9	4.3	2.6	220	104	38	5.1	2	3.1	30	0.9	123	4.5	25	1.93	C
22	72	24	2	2	33	42000	13.6	3.1	10.5	120	85	548	4.3	1.8	2.5	60	1	142	5	26	1.91	C
23	73	24	3	0	21.9	53000	12.4	8.8	3.6	28.3	33	765	5.8	2.4	3.4	105	3.3	133	5.4	14.9	1.2	C
24	73	25	2	0	21.7	136000	7	2.9	4.1	144	65	90	6.3	1.7	4.6	34	1	130	3.7	23.2	2.2	C
25	63	28	1	2	28	22000	3.9	1.2	2.7	476	208	214	5.9	2.6	3.3	128	3	126	3.7	18.6	1.2	C
26	70	26	2	2	31.4	17000	0.8	0.5	0.3	38	22	284	5.9	2.8	3.1	80	1.5	139	4.8	16.2	1.2	B
27	86	14	0	0	29	198000	3.8	1.4	2.4	189	120	303	7	3.1	3.9	19	0.8	128	3.5	19.6	1.33	C
28	75	23	2	0	29.7	59000	2.8	1.8	1	62	45	218	5.7	2.4	3.3	79	1.6	138	5.1	13	1.11	C
29	84	15	1	0	28	60000	2.8	1	1.8	80	69	448	6	2.7	3.3	70	1.2	130	5.1	24.1	2.1	C
30	80	16	2	2	34	80000	1.2	0.2	1	80	71	568	7	3.1	3.9	78	1.6	128	5.1	24	2.2	C

S No	HBsAg	Anti HCV	Urine R/M	Ascitic Protein	Ascitic Sugar	Ascitic Fluid TLC	Ascitic poly morphs	Ascitic Mono morphs	Blood Culture	Positive growth	Ascitic Fluid Culture	Ascitic Positive growth	Urine culture	Urine Positive growth	Pus Culture	Pus_ Positive Growth	SputumCulture	SputumPositive growth	Other Fluids Culture done	Other fluids growth	Bacteremia	SBP and its variants	UTI	Cellulitis	Pneumonia	Others	Infection
1	0	0	0	0.6	76	440	8	92	0	0	0	0	0	0	2	1	0	0	0	0	0	0	0	1	0	0	1
2	1	0	0	0.6	200	440	8	92	1	3	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
3	0	0	1	1.8	140	200	10	90	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
4	0	1	1	0.5	110	290	85	15	0	0	0	0	1	1	0	0	0	0	0	0	0	1	1	0	0	0	1
5	0	0	0	0.5	134	180	20	80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0.7	113	280	30	70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	1.4	120	280	30	70	0	0	0	0	0	0	0	0	2	2	0	0	0	0	0	0	1	0	1
8	0	0	1	0.5	90	250	30	70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
9	0	0	0	1	110	120	10	90	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0.9	120	170	20	80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0.8	124	50	8	92	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0.7	102	9600	92	8	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	1
13	0	0	0	0.5	111	130	30	70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	1	111	2000	2	98	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	1.2	96	540	75	25	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
16	0	0	0	0.9	131	400	40	60	1	3	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
17	0	0	0	1.3	140	220	40	60	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0.6	80	50	65	35	0	0	1	2	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
19	0	0	0	1.2	116	580	92	8	0	0	1	4	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
20	0	0	0	1	100	1200	92	8	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
21	1	0	0	0.6	140	160	5	95	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	1	0.5	106	350	75	25	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	1
23	0	0	1	1.1	235	2150	88	12	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	1
24	0	0	0	1.1	142	10	2	98	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	1.2	123	245	5	95	1	5	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
26	0	0	0	1.8	119	870	50	50	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	1
27	0	0	0	0.6	162	300	59	41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0.6	103	70	30	70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29	1	0	0	1	70	450	92	8	0	0	1	5	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
30	0	0	0	1.8	106	200	40	60	1	3	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1

31	Gopalakrishnan	M	58	1	1	1	90	16	99	1	1	0	0	0	1	0	2	3	8	10000	82	18	0	0	23.4	108000	2.1	1	1.1	37	43	178	5.8	2	3.8	116	2.2	138	3	29.4	2.8	C	0	0	1	0.9	120	280	8	92	0	0	0	0	1	2	0	0	0	0	0	0	0	0	1	0	0	0	1
32	Vijayakumar	M	38	1	0	0	82	20	98.4	0	0	0	0	0	0	0	2	2	10.7	600	80	16	0	4	30.4	60000	1.8	0.4	1.4	80	72	441	5.9	2.9	3	32	1	133	2.9	18	1.5	C	0	0	0	2.1	65	700	60	40	0	0	1	2	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
33	Raju	M	47	1	0	1	98	16	99	1	0	0	0	0	0	0	1	1	10.1	9000	68	28	3	1	28.9	27000	5.1	2	3.1	381	205	201	6.8	3.1	3.7	205	2.3	131	4.3	17.8	1.62	B	0	0	0	1.8	160	200	30	70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
34	Devaraj	M	30	0	0	0	90	16	98	1	0	1	0	0	0	0	2	1	9.7	20600	90	10	0	0	25.9	105000	15.8	9.7	6.1	398	580	255	5.8	3	2.8	23	0.8	125	2.7	16.7	1.45	C	0	0	0	1.2	105	700	10	90	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
35	Sahadevan	M	50	1	1	1	110	20	101	0	0	0	0	0	1	0	2	1	9.8	12300	76	20	3	1	26.8	64000	0.9	0.4	0.5	25	29	213	4.9	1.8	3.1	85	3	132	2.8	20.4	1.8	C	0	0	0	0.7	147	720	90	10	0	0	1	1	0	0	0	0	0	0	1	0	0	1	0	0	0	1	1
36	Muniyammal	F	25	1	1	0	90	18	97	1	1	0	0	0	0	0	2	1	9.8	23000	70	26	2	2	34.6	24000	0.8	0.3	0.5	21	25	157	6.4	3.2	3.2	16	0.6	129	3.9	26.2	2.48	C	0	0	0	1	139	180	40	60	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
37	Appadurai	M	66	0	0	0	104	20	99	0	0	0	0	0	1	1	2	3	11.4	5400	72	24	2	2	33	67000	1	0.4	6	95	49	221	5.1	2	3.1	214	3.6	134	5.6	12.2	1.07	C	1	0	0	1.1	108	340	20	80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
38	Kannan	M	45	1	0	1	96	16	98.4	1	0	0	0	0	1	0	2	2	11.2	9200	68	32	0	0	33	70000	1.6	0.4	1.2	80	71	225	5.4	2.9	2.5	49	1.2	130	4.4	15.4	1.3	C	0	0	0	1.4	130	170	30	70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
39	Palaniyamal	F	52	1	1	0	80	16	101.4	1	1	0	0	0	0	0	1	1	8	7200	82	18	0	0	25.1	60000	0.8	0.4	0.4	50	71	445	5.1	1.9	3.2	40	0.9	140	3.6	13.4	1.2	B	0	0	1	1.1	130	150	32	68	0	0	1	2	0	0	0	0	0	0	0	0	0	1	1	0	0	0	1
40	Gurusamy	M	60	0	0	1	98	16	99.6	1	1	0	0	0	1	0	2	2	8	12300	80	18	2	0	24.8	69000	1.4	0.4	1	40	31	180	6	2.7	3.3	70	1.3	129	5.4	16.4	1.4	C	0	0	0	1.1	140	540	92	8	0	0	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
41	Vinsent	M	48	0	0	1	86	18	98.6	1	0	0	0	0	1	0	1	2	11	8200	70	26	4	0	32.4	116000	0.8	0.2	0.6	41	30	160	6	3.1	2.9	41	1.1	130	4.6	15.4	1.4	B	0	0	0	0.9	110	110	30	70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42	Elumalai	M	61	0	0	1	90	16	98.8	1	0	0	0	0	0	0	1	1	10.7	9700	76	23	1	0	32	120000	0.8	0.1	0.7	80	43	221	6.8	3.1	3.7	23	0.8	135	3.6	14.3	1.3	B	0	0	0	1.4	101	130	35	65	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
43	Janagi	F	52	0	0	0	100	18	98.6	1	1	0	0	0	0	0	1	1	8.1	9700	70	24	4	2	25	80000	0.8	0.3	0.5	40	31	225	6	2.5	3.5	40	0.9	130	4.9	15.6	1.4	B	0	0	0	1.1	150	220	10	90	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
44	Santhanam	M	60	1	0	1	98	16	99	1	0	0	0	0	0	0	1	2	12.1	8700	71	26	3	0	35.6	110000	1	0.2	0.8	80	72	430	6.9	3.1	3.7	39	1.1	140	3.8	13.2	1.2	B	0	0	0	1	120	200	20	80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
45	Devi	F	54	1	0	0	110	20	101	1	1	0	0	0	0	0	2	3	8	14400	80	18	2	0	24.3	52000	1.4	0.4	1	37	41	205	5.9	2.6	3.3	39	1	130	5.1	15.6	1.4	C	1	0	0	1.2	107	300	90	10	0	0	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
46	Ponnusamy	M	60	0	0	1	90	16	99	1	0	0	0	0	1	0	1	1	12.1	9000	75	24	1	0	35	116000	0.8	0.2	0.6	74	60	200	6	2.8	3.2	23	0.6	130	4.4	13.3	1.2	A	0	0	0	1.2	110	150	40	60	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
47	Malliga	F	50	0	0	0	86	14	98.3	1	0	1	0	0	1	0	1	1	11.4	8600	70	26	2	2	33.1	120000	2.1	0.6	1.5	201	180	125	6.1	2.5	3.6	40	1.9	135	4.6	15.7	1.4	B	0	0	0	1.3	160	220	8	92	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
48	Raman	M	48	1	0	1	98	18	99.8	1	0	0	0	0	0	0	1	3	11	11600	82	18	0	0	32.1	80000	1.6	0.4	1.2	96	80	225	6	2.8	3.2	48	1.3	130	4.9	18.2	1.7	C	0	0	1	1.1	187	250	30	70	0	0	0	0	1	2	0	0	0	0	0	0	0	0	1	0	0	0	1
49	Kuppan	M	50	0	0	1	90	18	99	1	1	1	0	0	0	0	1	2	9	9900	62	34	4	0	26.7	68000	3.9	1.3	2.6	109	98	206	6.4	3.1	3.3	40	0.9	135	4.7	15.7	1.4	C	0	0	0	0.9	148	110	30	70	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0
50	Rajamanickam	M	68	0	1	1	98	16	98.4	1	1	0	0	0	0	0	1	2	8.9	9000	68	28	3	1	27	90000	1	0.4	0.6	40	38	131	6.4	3	3.4	28	0.6	134	3.4	14.3	1.3	C	0	0	0	1.2	130	138	32	68	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0